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THE SHATTUCK LECTURE

Changing Concepts and Practices in the Approach to Diseases of the Digestive Tract*

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BOSTON

ONE hundred and two years ago, at the age of seventy, Gerge Cheyne Shattuck, the elder, died in his house at the corner of Staniford and Cambridge Streets in the West End of Boston. Born in Templeton, the youngest son of Dr. Benjamin Shattuck, he was educated at Dartmouth. He received his M.B. from that institution in 1806, and in 1807 he received his M.D. from the University of Pennsylvania. From Dartmouth he received two honorary degrees — M.D. in 1812 and LL.D. in 1853. Harvard awarded him an honorary A.M. in 1807, the year in which he began to practice in Boston. He had a very large family practice and was well known for his benevolence and his contributions to his community. George Cheyne Shattuck had an extraordinary talent for writing medical papers and won the Boylston Prize for several successive years. In recognition of his professional standing, he was asked to deliver the annual discourse before the Massachusetts Medical Society in 1828 and was elected president of the Society for the years 1836-1840. At the Massachusetts General Hospital he was consulting physician from 1827 to 1846 and served on the Board of Consultation from that year until his death in 1854. He was one of the consulting physicians for the City of Boston. His was an abundant and generous professional life, and today we will do well to recall him as an eminent physician and as the second in five successive generations of very eminent physicians. His son, George Cheyne Shattuck, the younger, followed in his father's footsteps and was also elected president of the Massachusetts Medical Society. His two distinguished grandsons, Frederick Cheever Shattuck many in this audience. The present George Cheever and George Brune Shattuck, were well known to Shattuck, son of Frederick Cheever Shattuck, is an authority on tropical disease. Truly, this is a medical family that has contributed largely to medicine in Boston and Massachusetts for almost exactly a hundred and fifty years. The lengthened shadow of Benjamin Shattuck has indeed extended a far distance.

At his death in 1854, the elder George C. Shattuck left the sum of about $10,000 to the Massachusetts Medical Society to accumulate for three years and then to be held in trust for five years, at the end of which a third should be given to the Massachusetts Society for Promoting Agriculture, a third to the Massachusetts Charitable Mechanic Association and a third to the Massachusetts Medical Society. The income was to be used for "the collection and publication, annually . . . of historical or other essays on the climate of this commonwealth, on the diseases of its inhabitants, and on such other subjects as the said society or its government may select." No immediate action was taken by the Society until 1877, when the Council directed the Committee on Publications to offer prizes out of this fund for essays. The first year four essays were submitted — three of such merit that it was difficult to select the best. Accordingly, with typical New England economy, no prize was awarded; subsequently, no meritorious essays were offered, even when a prize of $1,000 was announced in 1885. Therefore, in 1888 the Council of the Society instructed the Committee on Publications to provide for a lecture, to be called the Shattuck Lecture, on a subject in accordance with the original bequest, the lecture to be delivered at the annual meeting of the Society. This, then, is the history of the origin of the Shattuck Lecture, which I have the honor to present at the annual meeting marking the hundred and seventy-fifth year of the Society. The first Shattuck Lecture was given in 1890 by George Brune Shattuck, grandson of the original donor, on the subject "Influenza in Massachusetts." The list of speakers who have subsequently appeared before this society over a span of fifty-five years is an imposing one. Therefore, it is with the deepest humility that I venture to submit certain thoughts and comments.

The facts that I shall present are primarily for the purpose of illustration, and to indicate the steady

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progress and changing concepts that have come with the accumulation of knowledge during the hundred-and-seventy-five-year life span of this society. At first progress was slow, but during the last four decades medicine in all its branches has progressed with extreme rapidity. It is during these four decades that one can observe the transition from what was essentially clinical teaching based on long experience and observation, as exemplified by the Shattucks, to an era of rapidly expanding scientific progress that is constantly being integrated into the care of the individual patient. This applies to practically every field of medicine, including that of digestive-tract disease and digestive-tract physiology. It is true, however, that progress has been somewhat slower and more uncertain in this particular field than in many others, chiefly because methods of relative precision have been more difficult to devise for the study of digestive phenomena than, for example, for investigation of circulatory disease, respiratory abnormalities, modifications of renal function and endocrine disturbances.

In very recent years numerous and intensive studies of gastrointestinal function have been carried out by many enthusiastic investigators, and much new information of clinical and scientific import is beginning to be assembled. The whole field of gastrointestinal physiology and disease, however, is still wide open to intensive study. Today, I wish to call attention to some of the advances in one aspect of this field — namely, gastric secretion and to suggest much that is still to be learned that will have direct clinical application.

Gastric Secretion

In the middle of the eighteenth century (1752), Réamur studied the physiology of digestion in birds and succeeded in isolating the gastric juice and in demonstrating its solvent effect upon foods. These results were confirmed and extended by the work of Spallanzani in 1782, a year after this society was founded. He discovered the digestive power of saliva and reaffirmed the solvent property of the gastric juice, showing that it would act outside the body and that it inhibited or prevented putrefaction. He failed, however, to recognize the acid character of the gastric juice, a point brought out by the American physiologist, John R. Young, in 1803. Young established that the acid in the gastric juice was not the product of fermentation in the stomach but was part of the normal gastric secretion. Prout, in 1824, proved that the acid was free hydrochloric acid. In 1833, William Beaumont, a surgeon in the United States Army, published his famous "Experiments and Observations" on an accidental gastric fistula in the Canadian halfbreed, Alexis St. Martin, which threw so much light upon the nature of the gastric juice, the process of digestion in the stomach and the early stages of gastritis. Beaumont also postulated some other active chemical substance produced by the stomach, which Schwann in 1835 proved to be pepsin. Thus, the first real contribution to gastric physiology was built up from scattered observations made from 1752 to 1835. The fact of acid-peptic digestion was established. Beaumont also proved again that the acid secretion of the stomach stopped putrefactive processes. This inhibition of bacterial growth by acid gastric juice has real and practical importance in modifying the initial insult to the peritoneum that follows the perforation of a peptic ulcer, as well as in affording some protection against ingested pathogenic bacteria. Furthermore, he established certain facts that until very recent years have been practically forgotten. With the assistance of Emmett, of the University of Virginia, he showed that acid gastric juice in a human being contained appreciable amounts of sodium, potassium, magnesium and calcium. Only in relatively recent years has full realization obtained of the important losses that occur as the result of persistent vomiting of fluid containing these essential substances. Also, his in vitro observations showed that the secretion of the stomach "when pure . . . is capable of being kept for months . . . possessing all of its original properties." Actually, he produced, in vitro, proteolytic digestion with a sample that had been kept for eleven months — a clear demonstration of enzymatic stability, with a specific action at an acid pH. An interesting recent observation on the action of pepsin is that this proteolytic enzyme may play an important part in the liberation of the vitamin B complexes from their natural combination with food proteins.

The demonstration of rennin, a lipase, and a urease in normal gastric contents is largely of academic interest. The urease has no proved digestive or other function and is probably derived from the urea-splitting organisms of the intestine. Rennin, which coagulates milk, acts at a pH that is much higher than that found in the adult human stomach and may be of physiologic importance only in infants who normally have a low acid gastric secretion. So-called gastric lipase may represent regurgitation into the stomach from the duodenum. Like rennin, it acts at an optimum pH that is much higher than that found in normal adult gastric juice and again, may have some physiologic action only in infants. The significance of gastric mucins will be discussed subsequently.

Of more immediate consequences to this discussion are the attempts to determine the mechanism by which the gastric secretion of hydrochloric acid and a proteolytic enzyme is controlled. This has required many decades to elucidate, and even today knowledge is incomplete, although a sufficient array of facts is available to be clinically significant. Beaumont's meticulous observations pointed out that local mechanical irritation of the gastric mucosa by an inert foreign body caused active secretion. This fact is still overlooked or insufficiently recognized by some clinical investigators, who at times fail to remember that

an inlying stomach tube may modify or even invalidate gastric secretory studies. The investigations carried out on St. Martin also demonstrated that anger produced mucosal hyperemia and increased acid secretion, a fact verified and more adequately studied, but not materially altered, by the careful observations made a century later by Wolff and Wolf.

In 1910 the great Russian physiologist, Pavlov, established beyond any doubt the principle of conditioned reflexes that is responsible for so-called psychic secretion. Taste, sight and smell are powerful stimuli for the initiation of acid pepsin secretion by the fundic cells of the stomach. These stimuli are carried over the vagi from higher centers in the nervous system. It is of more than incidental interest to recognize that vagal stimulation also causes a secretion of gastric mucin and neutral chloride. A second mode of action is that originally studied by Edkins in 1906 and considerably elaborated by many investigators since that time. In essence, it assumes, on what seems to be very adequate evidence, that the presence of food in the stomach causes the elaboration of a substance, gastrin, by the cells of the pyloric antrum, which by a humoral route stimulates the fundic cells to secrete acid and pepsin. This is called the gastric phase. A third, and still debated, mechanism involved in the gastric secretory process is based on the evidence of a so-called intestinal phase. With the passage of acid chyme into the duodenum, another secretogogue or hormone is thought to have been demonstrated, which by a humoral route also promotes a continuation of acid pepsin secretion.

Other factors influencing gastric secretion may be briefly mentioned. Hypoglycemia, which is due to long abstinence from food or to the overproduction or the injection of insulin, simulates the effects of psychic secretion. It acts apparently by central stimulation and is mediated largely over the vagi. The injection of histamine produces maximal acid secretion by the fundic cells, but very little pepsin. Whether histamine stimulation is a normal physiologic mechanism is still to be proved. Alcohol, water and certain other substances have an action similar to that of histamine. A further stimulation of acid production by the stomach has been clearly demonstrated by Gray and his associates — namely, that caused by ACTH and certain corticosteroids. These investigators have shown that in normal subjects the administration of ACTH or cortisone produced a marked increase in basal and nocturnal gastric secretion of acid. Whether there is an equivalent increase in the secretion of pepsin is at present open to question. Such studies suggest, however, that stress may profoundly affect gastric secretory processes, not only by direct stimulation over vagal pathways but also, indirectly, by affecting adrenocortical activity. Finally, mention should be made of certain other mechanisms that directly or indirectly affect or modify the secretion of acid and pepsin. Partial neutralization of acid can obviously be effected by salivary secretion and by regurgitated duodenal contents. Gastric mucin also is a fairly effective buffer and is secreted by the entire stomach, including the pyloric area. A humoral mechanism that appears to act as normal regulator of the secretory process in the stomach is that identified by Ivy and called enterogastrone. This substance is apparently elaborated by the duodenal mucosa as a result of the passage of gastric contents, especially lipid material, into the duodenum, with resulting inhibition or reduction of gastric acid production.

It remains to mention the production of certain protein substances by the gastric mucosa — the intrinsic factor of Castle, first described by him in 1929, and the mucins. Both are secretory products of the normal human stomach. The intrinsic factor, although not isolated in pure form, is derived in the human being from the cells of the corpus and fundus of the stomach. Central vagal stimulation normally increases the amount of intrinsic factor in gastric juice, as does the ingestion of meat and certain other substances. The accumulated evidence of careful investigators indicates clearly that this protein moiety is normally necessary for the assimilation of vitamin B_{12} to produce physiologic maturation of erythrocytes. At present the evidence points very clearly to the fact that its action is that of potentiating the intestinal absorption of vitamin B_{12}. In pernicious anemia, in which the gastric production of the intrinsic factor is essentially absent, the measured absorption of orally administered vitamin B_{12} by the intestine is negligible. The ingestion, by patients suffering from Addisonian anemia, of a concentrated preparation of intrinsic factor derived from normal gastric juice permits the absorption of orally administered vitamin B_{12}. This has been clearly demonstrated by Halsted and others in careful balance studies, using cobalt-labeled vitamin B_{12}. Thus a new and important principle has been added to the concept of gastric secretory physiology — namely, the secretion of a substance necessary for the optimal absorption by the intestine of another substance. Indeed, it is highly probable that other gastric secretory products will be identified that have for their function the optimal assimilation or utilization of specific nutritive elements by the small bowel.

Several other protein elements are secreted by the gastric mucosal cells that come under the general heading of mucins. One is the normal product of the secretion of the mucoid cells of the neck of the gastric glands in the fundus and corpus of the organ. This has been called gastric mucoprotein, or glandular mucoprotein, by Jerzy Glass, who believes that it may be identical with the intrinsic factor or may be combined with it. It is of interest that both substances appear to be similar in action and are absent from the secretions of patients with pernicious anemia. A second mucous component, gastric mucoproteose, is se-

creted by the columnar cells of the gastric epithelium and, unlike the mucoprotein, is present in patients with pernicious anemia. This substance is probably the degradation and dissolution product of the layer of protective mucus coating the gastric mucosa. These substances are still under intensive study by Jerzy Glass, Wolf and many other investigators.

Therapeutic Control of Gastric Secretion

This, then, is an approximate survey of our knowledge of gastric secretory activity as it is recognized at present. Some of the practical applications of these gradually accumulated facts may now be outlined, particularly as they apply to the therapy of peptic ulcer. Because of the close relation between ulcer formation and acid-pepsin secretion, numerous medical and surgical measures have been evolved to obtain a maximal control of secretory function. These are well known, but I shall endeavor to present them in a fairly orderly sequence.

Medical procedures aim primarily at a reduction in the excessive acid pepsin secretion in ulcer patients or in the partial neutralization of gastric contents. Control of esophageal, gastric and duodenal motor mechanisms I shall not discuss, although they, too, are of fundamental clinical importance. The proper use of sedatives or of a psychotherapeutic approach to the patient's problems undoubtedly cushions the effect of excessive psychic stimulation from higher levels of the central nervous system. Anticholinergic drugs, which now are legion, aim at the same result by blocking more or less effectively the excessive stimulation of fundic secretion during the so-called cephalic or psychic phase. Antacids raise the pH of the gastric contents to minimize peptic enzymatic activity, as do many food proteins that have a definite buffer value. Ingested fat, contained in milk, cream and other foods, passes slowly into the duodenum and causes the production of a substance that, by a humoral route, reduces acid pepsin secretion. The therapeutic feeding of mucin to protect the gastric mucosa and to buffer gastric activity was physiologically sound in principle but practically undesirable because of the disgusting quality of the material when ingested in effective amounts. Crude preparations containing "enterogastrone" have also been used in an attempt to inhibit excessive gastric secretory activity, but with very inconclusive results. The use of cation-exchange resins to absorb excessive hydrogen ions again has been of physiologic interest but has proved to be of no greater benefit than simpler and less expensive antacids. Diamox, which is said to inhibit the theoretical action of carbonic anhydrase in the over-all process of acid secretion, is of limited value and is probably undesirable as a therapeutic agent in patients with ulcer. Thus, the present commonly used medical measures are based on a gradually acquired scientific knowledge of gastric physiology. They constitute the basic principles in the treatment of peptic ulcer.

An entirely different nonoperative maneuver calculated to reduce gastric secretion is that of irradiation applied directly to the region of the stomach. This therapeutic measure, which has been carefully studied and evaluated over many years by Palmer and his associates, is based on the fact that therapeutic doses of x-rays produce atrophy of the gastric secretory cells, with a profound diminution in all secretory processes but mainly those affecting acid and pepsin. Careful serial gastric biopsies, as carried out by Wood, of Melbourne, Australia, have clearly demonstrated the gradual evolution of gastric atrophy under such exposure to x-rays. These atrophic changes persist for many months and are effective in producing minimal acid pepsin secretion for periods ranging from many months to several years. The general use of such a therapeutic measure is not to be recommended because of the possible effect on other important gastric secretions, such as the intrinsic factor, and also because of the potential danger of malignant degeneration, which may occur in persisting gastric atrophy, with damaged secretory processes. Nevertheless, it is highly probable that radiation therapy will be very effective and of extreme value in intractable ulcer situations in carefully selected patients in whom surgical intervention carries a prohibitive risk, or in those in whom radical surgery has proved ineffective.

The surgical approach to the ulcer problem has followed the same general fundamental considerations of secretory control but has undergone a series of changes since the first gastrojejunostomy was performed by Wolfler, of Prague, in 1881. Step by step, successive changes have been made, with important and interesting clinical results. Disregarding the amazing technical advances that have been made in modern digestive-tract surgery, I shall now comment on some of the modifications that have been evolved in the last seventy-five years.

Gastrojejunostomy, perfected and popularized by Moynihan, succeeded in partially diverting acid pepsin secretion from the ulcer-bearing area, and at the same time modified gastroduodenal motility. The operation failed to protect the jejunal anastomosis adequately from peptic digestion, and reactivation of the original ulcer or stomal ulceration occurred in a high percentage of cases, with the occasional added serious complication of gastrojejunocolic fistula.

A second attempt physiologically to control the effect of hypersecretion was based on two facts: the knowledge that hydrochloric acid is produced by the cells of the body and fundus of the stomach; and the realization that one important stimulus to this acid secretion is the passage of food over the antral segment — the so-called gastric phase. The operation of antral resection, originally performed by Billroth in 1881, has been gradually extended by subsequent

surgeons to the present radical subtotal gastrectomy, a procedure that has resulted in a reduction of gastric acidity to reasonably benign levels by effectively controlling the gastric secretory phase. This radical procedure has reduced the occurrence of stomal or jejunal ulcer to a very low figure. Unfortunately, radical subtotal gastrectomy has been followed in about 15 per cent of patients by important symptoms, commonly known as the dumping syndrome, or by serious nutritional difficulties apparently due to important interference with certain absorptive processes in the intestine, notably the absorption of fats. In unusual cases, this interference with fat absorption may result in fecal losses as high as ten to fifteen times those occurring normally. The cause of the latter phenomenon is still not clear, but it is possible that it may be due to the removal of an important antral secretion that is necessary for the optimal absorption of fat and possibly of other substances.

The Billroth I gastroduodenostomy may in part obviate the nutritional problems attendant upon the Polya type of subtotal gastrectomy, but in the experience of most surgeons, this maneuver is less successful in preventing ulcer recurrence unless a full 75 per cent resection is performed (Harkins). Theoretically, gastroduodenostomy does not prevent the passage of gastric contents directly into the duodenum, thereby failing to control the so-called intestinal phase of gastric secretion.

A later concept is that introduced in 1943 by Dragstedt, and very shortly thereafter by Moore, of vagal resection, in the hope that this procedure would effectively nullify the frequently observed and obvious effects of emotional tensions on secretory processes. This operation clearly was aimed at completely removing the psychic phase of secretion, a therapeutic measure that had long been attempted medically by the use of atropine or its derivatives. Careful studies indicated clearly that acid pepsin secretion was tremendously diminished after vagotomy, with accompanying reduction in gastric motility. This procedure alone did not suffice, in part because it did not control the gastric secretory phase, and in part because of awkward situations arising from reduced gastric emptying in the presence of even minimal cicatricial obstruction. These difficulties were obviated somewhat by the addition of the procedure of gastrojejunostomy to vagal section, thereby diverting an important part of the gastric food contents from the antrum and also from the duodenum. A more recent modification has followed — namely, the procedure employed by Weinberg and by Dragstedt of a pyloroplasty in place of a gastrojejunostomy, which reduces the possibility of antral stasis in the presence of any degree of obstruction or in the absence of normal gastric emptying, and so far has seemed to add to the effectiveness of the operation.

Two other developments that should be mentioned are also based on sound physiologic reasoning. Both aim at obtaining control of the cephalic phase of gastric secretion, and at the same time at preventing the gastric phase and possibly the intestinal phase. The first operation is that of a modified subtotal gastrectomy combined with vagal section, as performed by Smithwick. The second procedure consists in a vagal section and transection of the body of the stomach, with antral exclusion and a gastrojejunostomy, as recently introduced by Waddell.

All these successive modifications have been based on careful animal experimentation and adaptation of proved physiologic principles to human surgery. The history of gastric surgery makes it perfectly clear that many years must elapse before a complete evaluation of any given procedure can be adequately achieved. To date, no surgical procedure has obtained complete control of the various phases of gastric secretion that I have outlined above. Various objections to any given maneuver can properly be made on the basis of subsequently acquired knowledge, and it is evident that the perfect gastric operation in the treatment of peptic ulcer is yet to be evolved. The fact remains that successive increments to our knowledge, based on continuing and careful investigation and experimentation, have resulted in increasingly effective measures in cases in which surgical intervention becomes necessary.

Against this increasingly successful surgical control of ulcer recurrence must be placed the dislocation of normal physiologic events that results from such procedures. Mention has already been made of the nutritional problems associated with radical resection and anastomotic operations. An additional recent interesting observation is that of the occasional troublesome diarrhea that follows any of these procedures, possibly most frequently in association with vagal section in conjunction with a gastrojejunostomy. Careful stool culture in some of these cases has shown the previously unsuspected presence of salmonella organisms, which may well have been responsible for increased bowel activity and which have, in a few cases, responded to proper antibiotic therapy. The cause of such an occurrence at present is speculative, but it is possible that the loss of gastric acidity as a protective mechanism against ingested bacteria may be the explanation. Further study of this rather unexpected phenomenon may well be rewarding.

Of equal or greater importance may be the results of future investigations of the cause of malabsorption syndromes secondary to gastric resections. Indeed, the entire mechanism of intestinal absorption requires intensive and continuing exploration by critical investigators to determine the as yet little understood processes involved in the passage of various substances across the intestinal mucosal barrier. The importance of such studies cannot in any way be overestimated.

Discussion

That which has been accomplished over the years

in the gradual acquisition and integration of the basic facts in a given field of medicine has been illustrated by the foregoing recital of progress in the study of gastric secretory physiology. This has involved the combined effort of clinicians, clinical investigators and basic scientists and has demanded imagination, the willingness to speculate, close observation of clinical facts and repetitious experimentation. With the advent of the rapidly increasing number of scientific and more accurate methods of research, we are inevitably approaching the infinitely small but very specific systems that exist in individual cells and that determine organ function. We may look with confidence to the day when gastrointestinal function can be spelled out with greater precision and with a greater chance of controlling or correcting the various abnormalities that underlie the clinical manifestations of disease in this important system. Therefore, I wish to stress certain attitudes that I consider of great importance and believe to deserve continuing emphasis.

It is particularly true in the field of gastroenterology, which, after all, is but a branch of medicine, that a clear understanding of digestive-tract problems can be obtained only by the closest possible collaboration between practicing clinicians and laboratory investigators, and also between the two major groups in the profession — namely, those interested primarily in internal medicine and those interested primarily in surgery. Very few of the problems under discussion can be classified as being strictly medical or strictly surgical. In the majority of cases the problem presented by an individual patient with digestive-tract symptoms may at any time require consideration by both the internist and the surgeon. Only too frequently members of the profession are unwilling to work as a team on a given problem, the attitude being that it should be resolved solely by either a surgeon or an internist, but not by both. Such an attitude has been very harmful in the past and has too often resulted in totally unnecessary or unphysiologic surgery, or in catastrophic and tragic events due primarily to the fact that a medical practitioner was reluctant to avail himself of the services of a thoughtful, well trained surgeon. I should like to emphasize again that there is practically no field in medicine in which close correlation is more necessary for thoughtful and productive work than the field of digestive-tract disease. Mutual confidence and cooperation must provide the essence of successful therapy and well co-ordinated thinking.

A second thought that I wish to stress is the too frequent dichotomy that resolves itself into a controversy over whether a concept or a procedure is either scientific or practical. To be sure, fundamental basic scientific research frequently deals with abstractions, at least for a time. It is nearly always true, however, that as these abstractions become integrated with clinical thinking, they represent practical and frequently most valuable contributions to the care of individual patients in one or another of the many complex situations that so often arise. For this reason, I earnestly desire to urge a greater and more adequate understanding between so-called academic or investigative groups, which are concerned primarily in searching out basic mechanisms and basic causes, and those who are primarily interested in the care of patients. There should be no real difference between the goals of the two groups. The closer they can be welded, the greater will be the benefit to the individual patient and his problems. Whatever is truly scientific can eventually be applied in a practical fashion to one or another of the many facets of medical and surgical problems. Indeed, it is quite obvious that a large number of the recent advances in all fields have not only added to our knowledge of fundamentals but also made it possible for medical science to do things for the individual sick patient that even a decade or so ago were believed to be utterly impossible.

A third consideration lies in the fact that, for the most part, advances in knowledge are going to come from highly trained younger men. It is to them that we must give our enthusiastic support and co-operation, to create the atmosphere that promotes further and continuing progress in the understanding and the handling of complex bedside problems. It is equally true that again and again the younger man who is highly trained needs the balance and the clinical experience that only a wise and critical older practitioner can supply. The latter can frequently point out the problems that are encountered daily at the bedside and can stimulate further search for additional information at a very fundamental level. The necessity of combining the experience of the older and observing clinician and the enthusiasm of the young scientist is implied in Galileo's words, which will always be valid: "It is so very easy to seek the significance of things in the *papers* of this or that man, rather than in the *works of nature* which, ever alive and active, are constantly before our eyes."

Personally, I have great faith that all the aims that I have mentioned can be achieved. Closer relations between internist and surgeon, between investigator and practicing physician, and between the older and younger man in the profession can be developed and maintained. With the continuing accumulation of new scientific facts, clinical application to human problems can be so critically scrutinized by each of these groups that the science and practice of medicine become one. It can be added without hesitation that when these aims are accomplished, the community, as represented by individual patients, will benefit tremendously. We should not forget the advice of Pope in his *Essay on Criticism*: "Be not the first by whom the new is tried, nor yet the last to lay the old aside."

SERUM PROTEIN ALTERATIONS IN UREMIA*

II. Elevated Alpha-2 Globulin in Patients

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SAN FRANCISCO

ATTEMPTS to correlate the clinical course of uremic patients with changes in certain serum constituents have been unsuccessful.[1] Similarly, efforts to link the development of uremia to specific "toxins" have been inconclusive.[2,3] To date, no etiologic factor has been identified for the uremic state[4] — irrespective of any possible relation between diverse mechanisms that terminate in uremia — that is, "renal failure with retention of nitrogenous catabolites."[5]

In a previous study reported from this laboratory, uremia was produced in dogs by bilateral ureteral ligation.[6] In these animals it was demonstrated by filter-paper electrophoresis that prolongation of the uremic state effected a distinct elevation of serum alpha-2 globulin. Whether such an alteration occurred in the serum of uremic patients was not known. A further study was then undertaken to determine whether a similar alteration occurred in the serum of uremic patients. The findings of the latter investigation constitute the basis of this report.

MATERIALS AND METHODS

The clinical laboratories of several hospitals in San Francisco co-operated by providing us with serum specimens whenever a serum nonprotein nitrogen above 40 mg. per 100 ml.[7] or blood urea nitrogen[8] above 20 mg. per 100 ml. was encountered. Filter-paper electrophoresis was performed in our laboratory on such serums, according to the technic described below. Concomitantly, the patient's history, therapy and clinical course were correlated.

Serum samples were studied within one to five days after being drawn from the patient. Reanalyses of certain specimens within thirty days of refrigeration at 40°C. revealed no apparent alteration of the electrophoretic pattern of alpha-2 globulin. Serum creatinine determination was also done[9] on specimens from 34 of the 47 patients included in this report. On serums of 20 of the 47 patients, albumin and globulin determinations were performed.[10] In all, electrophoretic patterns were made of 94 serum samples, including 10 cases in which two or more drawings of blood from the same patients were taken either days or weeks apart.

The apparatus for filter-paper electrophoresis is Model No. 1404, constructed by the Research Specialties Company of Berkeley, California. It consists of two Lucite vessels that support a plastic tray ridged to carry a strip of filter paper 11 by 51 cm. This entire unit is covered by a sheet of plate glass.

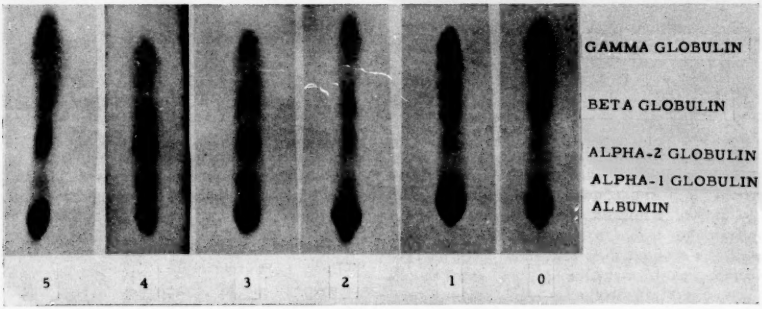

FIGURE 1. *Range of Serum Alpha-2-Globulin Levels.*
The classification, determined by visual comparison of stain intensity of electrophoretic pattern, progresses from "0" (subnormal) to "5" (maximum elevation).

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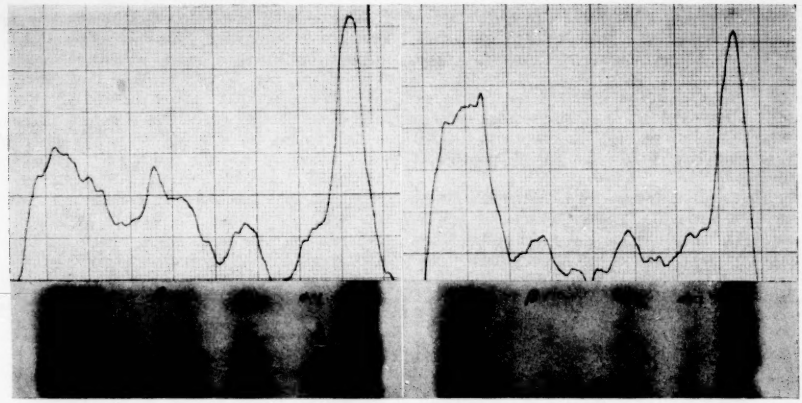
The electrodes are nonreactive stainless steel, energized by a Model No. 1910 power supply operated off standard-line voltage.

The operating principles in performance of electrophoresis throughout this study were the same as those described by Osserman and Lawlor.[11] Four serum specimens, each of 2-lambda volume, were applied to the same Whatman No. 1 filter-paper strip for a typical electrophoretic migration. The filter-paper strip was washed in buffer solution, blotted free of excess buffer and allowed to equilibrate at 500 volts with 3 or 4 milliamperes of current for about thirty minutes before application of the serum samples. We achieved best resolution of serum protein components by maintaining a constant 500-volt, variable 3-5-milliampere current for five or six hours, using a 0.09-molar veronal buffer, at pH 8.6, in 12 per cent propylene glycol at room temperature.* (The propylene glycol served to minimize distillation from the filter paper.) Bromphenol blue was applied to the serum specimen before electrophoresis was started, to visualize the migration of protein — namely, the dye preceded the albumin. After electrophoresis, the filter-paper strip was blotted and dried at 80°C. and then stained while still warm in a saturated solution of Buffalo Black† in 40 per cent ethanol and 10 per cent acetic acid for ten minutes.[12] The strip was then washed repeatedly in the ethanol and acetic acid mixture to remove excess dye and, finally, blotted dry.

*The conditions of the electrophoresis that proved optimal were arrived at by varying buffer concentration (0.05-0.1 molar), duration of migration (four-twelve hours), current (2-10 milliamperes) and voltage (100-500 volts).

†Available from National Aniline Division, New York City.

Interpretation and classification of the intensity of the stained alpha-2 area on the filter paper were *qualitatively* established by numerous reviews with the naked eye of all the patterns until we reached agreement for each electrophoretic pattern. Figure 1 shows the arbitrarily designated groups of stain intensity of alpha-2 component. Multiple serum specimens drawn from healthy subjects on different occasions were used as the normal-level base line.



A B

FIGURE 2. *Quantitative Photometry of Alpha-2-Globulin Stain Intensity in Patient E.R.*
A demonstrates Group 4 elevation of the serum alpha-2 globulin. As the disease progressed the alpha-2 globulin dropped to a Group 2 level (B). *No direct comparison was possible between the base lines of* A *and* B *owing to variable background staining, as a result of "trailing" phenomenon.*

A complete grouping of the degrees of change of serum alpha-2 globulin as formulated for this study is as follows:

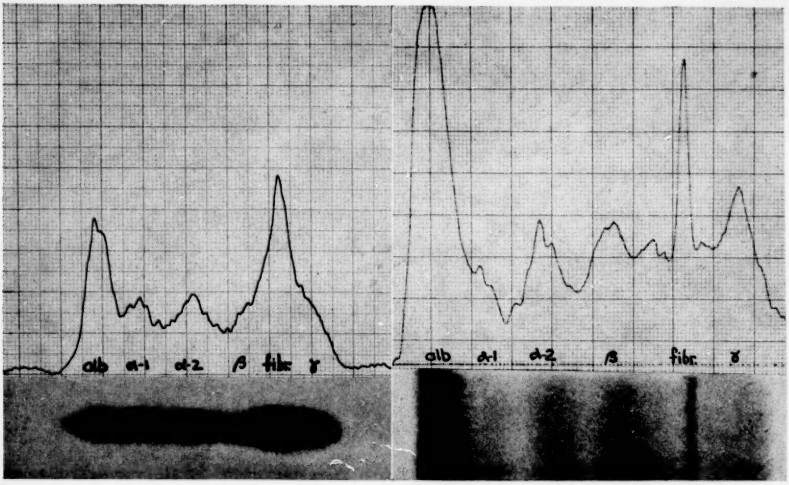
Group 0: subnormal level.
Group 1: normal level.
Group 2: slightly elevated level (Fig. 2*B*).
Group 3: moderately elevated level.
Group 4: sharply elevated level (Fig. 2*A*).
Group 5: extremely elevated level.

It is emphasized that no quantitative comparison of these 94 electrophoretic patterns was attempted. Several random determinations were performed with the Spinco "Model R Analytrol" photometric scanner for the purpose of validating classification by the naked eye, but no standardization of this technic was undertaken. Therefore, differences in completeness of protein resolution resulted in artifactitious base lines. This partial resolution, essentially a "trailing" of the migratory front, accounts for "background area" of increased stain *between* bands.

To demonstrate the similarity of electrophoretic separation of the same serum sample by two different instruments, photometric curves of the migratory pat-

terns are compared in Figure 3. The section in Figure 3*A* was made by our regular apparatus, whereas that in Figure 3*B* was produced by the Spinco unit.

Several electrophoretic patterns were selected to demonstrate representative results (Fig. 4). As standards of reference, previously demonstrated in Figure 1, specimens of "subnormal," "normal" and "extreme elevation" of alpha-2 globulin were selected at random and incorporated with the results of the previously unclassified "test serums" in Figure 4.



A B

FIGURE 3. *Qualitative-Quantitative Electrophoretic Pattern of the Same Serum Specimen. Different slit widths were used to scan* A *and* B *photometrically. The curves are comparable. Visual classification is manifestly easier with* A, *which exemplifies the type of pattern used throughout this study.*

RESULTS

Of the 47 patients, ranging in age from five to eighty-eight years, 44 were males, and 3 were females. Table 1 represents an aggregation of the subjects' ages, serum nonprotein nitrogen (or blood urea nitrogen), creatinine values and albumin-globulin ratios as related to variation of uremic serum alpha-2 globulin.

In the foregoing figures, a rough correlation is apparent between quantitative value of nonprotein nitrogen and elevation of serum alpha-2 globulin. As suggested below in the discussion, the pathologic change in the renal parenchyma is perhaps the determining factor in degree and extent of rise of serum alpha-2 globulin in uremia.

A general relation appears to exist between the level of serum creatinine and that of alpha-2 globulin. Serum creatinine was elevated twice as often (23 cases) when serum alpha-2 globulin was elevated as when the latter component was normal.

Although the over-all levels of serum protein did not seem to be basic to alterations in uremic serum alpha-2 globulin, a surprisingly high incidence of reversed albumin-globulin ratios was manifest. Since these ratios were distorted by albumin *and* by globulin alterations, one can only observe that major disturbances in protein metabolism apparently ensue. Specifically, in our study, 13 out of 20 patients had reversed albumin-globulin ratios, with elevated serum alpha-2. This could conceivably suggest some major alteration in protein metabolism of which elevation of serum alpha-2 globulin might be either a primary or simply an indicial feature. Scheurlen[13] postulated that fundamental alterations in protein metabolism occur in certain diseases. Our results in uremia tend to support this thesis.

The type or stage of a uremia-producing disease appeared to be the most critical factor in elevation of serum alpha-2 globulin. As shown in Table 2, impairment of renal function, which was consistently present, afforded a standard of evaluation and determined the headings, "obstructive," "parenchymal" and "extrarenal." As noted, prolonged or irreversible obstruction could lead to parenchymal (functional) damage, as could extrarenal azotemia.

*Functional impairment of the renal parenchyma,**

*Disturbance of renal function was appraised, in most cases, either by marked decline in two-hour phenolsulfonphthalein excretion or by obvious diminution in excretion of radiopaque dye by intravenous urography and by acidotic imbalance of serum electrolytes.

either as the primary disorder or as a sequel to the basic disease mechanism, was associated with the greatest number of specimens containing increased serum alpha-2 globulin. Of the 45 patients included in Table 2, 17 of 23 (74 per cent) with parenchymal damage possessed serum alpha-2 globulin within Groups 3 to 5. Surprisingly, 10 of 12 patients with tients reported here. Relevant data are incorporated in Table 3. In 2 patients, who were young brothers, congenital bladder-neck obstructions had produced marked hydroureteronephrosis and thus uremia. Both children were successfully relieved by open surgical revision of the bladder neck.[14] As clinical improvement was observed, attested by a decline in nonpro-

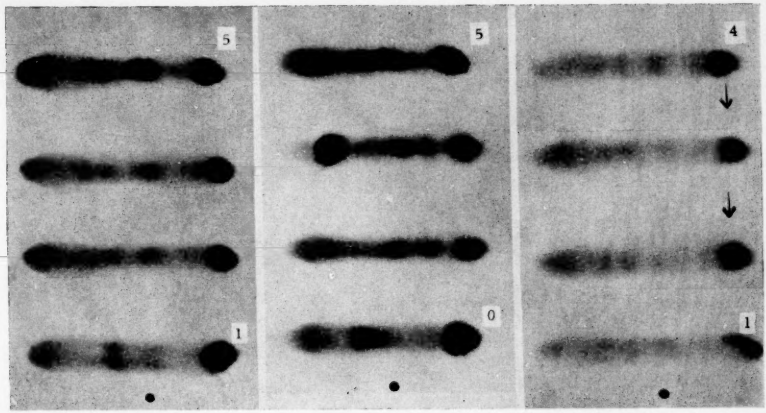


FIGURE 4. *Typical Demonstrations of Serum Electrophoretic Migrations (the Dots at the Bottom of the Three Records Locate Alpha-2 Globulin).*

A *contrasts Groups 5 (top) and 1 (bottom) with patterns of 2 different serums drawn a week apart from a patient with chronic glomerulonephritis. Each specimen was classified as Group 2, having demonstrated no change.*

B *contrasts Groups 5 (top) and 0 (bottom) with serums from 2 different patients. The specimens were defined as Group 4 (L.F.) and Group 3 (A.T.). Note the markedly elevated gamma globulin commonly observed in multiple myeloma, as a result of which L.F. was uremic and terminal (see Table 3).*

C *depicts Groups 4→1→0, different serum specimens from the same patient (S.H.), as compared with "base line" Group 1 (bottom), revealing a decline in alpha-2 globulin as clinical improvement occurred.*

extrarenal disease manifested an appreciable increase in serum alpha-2 globulin. Since serum specimens were collected during variable stages of a disease, and in some cases only 1 or 2 samples were taken from the patient, these data are of expositive rather than statistical value.

Only an exceptional serum specimen fell into either extreme grouping, "0" or "5."

Nineteen patients in the present series had cardiac disease in addition to uremia. In 10 of these, cardiopathy was the fundamental process responsible for the uremia; in 9 cases cardiac decompensation (mainly of arteriosclerotic origin) was an accessory finding. Of the 10 patients just mentioned, 5 had notable elevations of serum alpha-2 globulin (Groups 3 to 5), and the serums of the other 5 showed normal or minor increase of the alpha-2 globulin (Groups 1 and 2).

Three or more separate serum specimens were studied electrophoretically for alpha-2 globulin status during the course of the illness of 10 of the 47 patein nitrogen, acidosis and anemia, the serum alpha-2 globulin correspondingly dropped from Group 4 to 2. In 1 hypertensive patient, a middle-aged man who suddenly and inexplicably became profoundly uremic and died within a month, the serum alpha-2 globulin rose from Group 1 to Group 3, although the blood urea nitrogen remained relatively constant at 28 and the creatinine at 2.5 mg. per 100 ml. Contrariwise, in a fifty-four-year-old man with a three-year history of multiple myeloma, no change in serum alpha-2 globulin occurred in the terminal week of life whereas the blood urea nitrogen reached the impressive figure of 146 mg. per 100 ml. However, alteration of protein metabolism in multiple myeloma is so extensive and so inadequately understood that no conclusion can be drawn from this observation.

In the remaining 6 patients (of the 10 with multiple serum protein patterns) no elaboration upon the findings beyond the notes of Table 3 appears necessary, since the change in serum alpha globulin was insignificant.

Discussion

Interest in observing serum alpha-2 globulin levels in uremic patients followed our detection of this elevated protein fraction in dogs subjected to acute ureteral ligation.[6] Obviously, fundamental differences exist between uremic states experimentally induced in animals and those of the *patients* whose serums were used in the present study. Usually, within a period of days to weeks, acute mechanical obstruction to human renal function was surgically relieved. In the experiments on dogs, ureteral obstruction was intentionally produced and allowed to continue to fatal termination.

That one cannot anticipate results in human disease from data derived from animal experiments was borne out in the present study. Elevation of serum alpha-2 globulin was inconstant and sometimes surprisingly at variance with our expectations, in contrast to the consistent rise in the experiments on dogs.[6] Not only were different diseases encountered in the human subjects but also different stages of the disease were in force when serums were obtained for study. For example, in 2 cases of obstructive uropathy with well elevated serum nonprotein nitrogen, no elevation of serum alpha-2 globulin was found (Table 3). This simply emphasizes the well known clinical observation that no relation exists between the numerical value of serum nonprotein nitrogen and the clinical manifestations or degree of uremia. Although a comparable disparity could exist between serum alpha-2 globulin and the clinical course of uremia, our data only reveal a seeming parallelism between serum alpha-2 globulin and the increased nonprotein nitrogen.

By way of definition for purposes of this study uremia is regarded as the clinical state characterized primarily by disturbances of nitrogen metabolism and of fluid and electrolyte balance, whether the basic cause is renal or extrarenal — that is, "prerenal azotemia."

It is not known whether the metabolic changes provoked during uremia lead to formation of a new "toxin" or of an unidentified catabolite that the kidneys cannot excrete. A similar dilemma was recently cited by Putnam[15] in his evaluation of pathologic serum globulins in multiple myeloma (the lack of conclusive data on this point is referred to below). Furthermore, in uremia, it is not known whether certain critical metabolic alterations would be reflected in the serum proteins or in the electrophoretic migrations of these proteins. From the present observations, it can only be suggested that *parenchymal* damage to the kidneys seems to be more regularly associated with an increase in serum alpha-2 globulin than *obstructive* renal disease.

From the data reported here, no clear relation can be drawn between progression of renal parenchymal disease and alteration in the serum alpha-2 globulin. In this series, a distinct trend in level of serum alpha-2 globulin was demonstrated in only 3 of the 10 patients from whom 3 or more serum samples were studied — namely, a decrease after clinical improvement and an increase with deterioration. However, most specimens were drawn only days or several weeks apart, whereas longer periods might have been necessary to detect actual change in the development of the disease. In this connection, it should be recalled that the clinical course of uremia is usually relatively short. Therefore, it is conceivable that detection of serum alpha-2 globulin alterations of appreciable magnitude was unlikely in a study such as ours or that these protein alterations are unrelated to the basic disorders involved in uremia. Scheurlen[13] and Lutterotti,[16] in studies of cardiac, hepatic or nephrotic illnesses in which the diseases are protracted or chronic, recorded greater changes in alpha-2 globulin. Similarly, in serums of patients with certain chronic, extensive

Table 1. *Patients' Ages and Certain Serum Analyses in Uremia.*

Alpha-2 Globulin	No. of Patients*	Average Age	Blood Urea Nitrogen or Nonprotein Nitrogen Increased†	Blood Urea Nitrogen or Nonprotein Nitrogen High‡	Creatinine§ Increased¶	Creatinine§ High‖	Albumin-Globulin Ratio** Normal	Albumin Normal Globulin Decreased**	Albumin-Globulin Ratio** Reversed
			no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases
		yr.							
Increased	33	53.9	8	25	10	13	3	2	13††
Normal	12	54.6	4	8	8	3	0	0	2

*Two of total of 47 patients (E.R. & I.J.) excluded from this table because of marked change in level of alpha-2 globulin between serum specimens at different dates (see Fig. 1).
†Urea nitrogen 20-40 & nonprotein nitrogen 40-60 mg./100 ml.
‡Urea nitrogen >40 & nonprotein nitrogen >60 mg./100 ml.
§Determination made in 34 patients.
¶1.5-3.0 mg. per 100 ml.
‖>3.0 mg. per 100 ml.
**Determination made in 20 patients.
††Ratio reversed in 13 cases because globulin elevated & albumin low, rather than normal albumin with elevated globulin.

skin diseases, Lever and Hurley[17] reported quantitative increase in serum alpha-2 globulin, as determined by cold ethanol fractionation and high-speed centrifugation.

TABLE 2. *Influence of Type of Renal Impairment on Serum Alpha-2 Globulin.*

TYPE OF IMPAIRMENT	NO. IN GROUP 0	NO. IN GROUP 1	NO. IN GROUP 2	NO. IN GROUP 3	NO. IN GROUP 4	NO. IN GROUP 5
Obstructive		2		3	3	1
Obstructive ——→ parenchymal			1	2	4	
Parenchymal			5	5	4	1
Extrarenal ——→ parenchymal					1	
Extrarenal	1		2	4	6	

Thus far, attention has been directed toward theoretical substances *extrinsic* to and perhaps distant from the kidney as responsible for elevation of serum alpha-2 globulin. Likewise, allusion was made to the possibility of modification within the kidney of such substances, delivered by the blood stream. However, *intrinsic* factors within the renal parenchyma must be considered, such as the status of the parenchymal blood vessels, their hydrostatic pressure and their physiologic adaptability. In the group of patients included in this report, there was a suggestive relation between cardiac decompensation and heightened serum alpha-2 globulin. The role of cardiac status in serum globulin alterations has been emphasized by other workers.[16,18,19]

Our finding of a sizable number of increases in alpha-2 globulin in extrarenal disease, presumably without renal parenchymal damage, points up the dual control of serum protein pattern — that is, the production of proteins as contrasted with rate and efficiency of nitrogen metabolism. It is theoretically possible for an extrahepatic source of globulin production to become activated or overstimulated in certain pathologic states.

After our preliminary disclosure of elevated serum alpha-2 globulin in uremic patients, a thorough search of recent related literature was undertaken. It was established that no similar study has been reported on uremic serum. Pertinent publications appeared most commonly in foreign journals. Much of the present discussion therefore involves a review of European electrophoretic investigations upon serum and urine during the past five years.

Reports by Scheurlen,[13] Lutterotti[16] and Zsótér and Pintér[18] in the German literature cited electrophoretically measured alterations of serum protein, particularly of the notably sensitive alpha-2 globulin fraction, in conditions such as cardiac decompensation, chronic inflammatory disease, some malignant tumors and lipoid nephrosis. It was also reported that filter-paper electrophoresis was a dependable, clinically practicable test.[19] Proposals were made for extensive trial of this technic in differential diagnosis between cardiohepatic decompensation and endocarditis[16] or among various cardiopathies.[20] Repeated electrophoretic analyses of serum protein have proved useful in the tracing of restoration of cardiac compensation that occurs during digitalis therapy.[13,16]

Prominent among the French reports of electrophoretic demonstration of alpha-2-globulin alterations are those of Jayle and Boussier,[21] who coined the term "haptoglobin." This refers to a mucoprotein, first found electrophoretically in the alpha-2 fraction of the serum and urine of a young nephrotic girl, and subsequently discovered in other patients.[20] The physical properties, component parts and immunochemical behavior of this globulin were investigated.[22] Other French workers, Raynaud, Robert-D'Eshougues and Pasquet,[23] cited serum electrophoretic studies in 20 nephrotic patients, noting both a relative and an absolute increase in the alpha-2 fraction. They distinguished fast-moving and slow-moving globulins in nephritic and nephrotic serums but preferred lipidograms to protein electrophoresis in differentiating lipoid nephrotic serum from that of chronic glomerulonephritis. The very sharp rise in "nonhaptoglobin alpha-2 globulin" was elsewhere cited as pathognomonic of lipoid nephrosis.[20] In contrast to the consistent elevation of serum alpha-2 globulin in the 20 nephrotic patients of Raynaud et al.,[23] Lever and Hurley[17] found normal serum levels of alpha glycoproteins by alcohol fractionation technics in 8 nephrotic patients.

Some related reports were found in the American literature. Putnam[15] recently summarized electrophoretic and chemical studies by his group on urine and serum of patients with multiple myeloma. Chemical characterizations of N-terminal amino acids of some abnormal serum proteins suggested that ". . . . structurally abnormal forms of serum globulins are synthesized in response to the disease." Passing attention was given to cryoglobulins, unnatural proteins found only in disease and most often in serum of patients with multiple myeloma. The cryoglobulins are perhaps basic to certain clinical manifestations of increased blood viscosity in some illnesses, but Putnam speculated that they may occur physiologically in trace amounts. Finally, Putnam[15] indicated that Bence-Jones urinary protein is synthesized *de novo* from the amino acids of the body pool and is rapidly excreted by the kidney, rather than formed from renal cleavage of unnatural serum globulins, a concept that has potential bearing upon our own theorizations.

Osserman and Lawlor[11] have pointed up characteristic protein abnormalities by paper electrophoresis of serum and urine of patients with multiple myeloma. They suggest that filter-paper electropho-

retic analysis of urine constitutes a simple and reliable diagnostic criterion of multiple myeloma and thus is feasible for routine clinical use.

By electrophoretic identification, King[24] found globulin to be the predominant fraction lost in patients with severe orthostatic proteinuria. It is interesting to conjecture upon the physiologic relation suggested by King's explanation of renal tubular overloading in the reabsorption of protein in orthostatic proteinuria and the comment by Boyce, Garvey and Norfleet[25] that "uromucoids" are secretory products of the epithelial cells in the collecting portion of the urinary tracts of patients with calcigerous urolithiasis.

Serial observations of the course of a disease are specified by Wall[31] as a primary value of electrophoretic study of serum globulins. In contrast, Arrigoni and Nava[32] question the clinical interpretability of multiple electrophoretic analyses. Available and growing evidence favors the conclusion of Wall and his colleagues, who have been able to ascertain "excellent correlations" for more than two and a half years between clinical aggravation of Hodgkin's disease and rise in alpha-2 globulin in over 400 serum specimens from 120 patients. Conversely, a qualitative decline in alpha-2 globulin was noted as remissions developed. Although uremia in most cases progresses to a fatal outcome more rapidly than Hodgkin's disease, our group will follow Wall's recommendation in the form of studying repeated electrophoretic analyses of the serum of nephrotic children and patients with toxemia of pregnancy.

TABLE 3. *Electrophoresis of Multiple Serum Specimens in 10 Cases.*

PATIENT	DISEASE	AGE	CLINICAL STATUS	NO. OF SPECIMENS	SERUM ALPHA-2 GLOBULIN	COMMENT
M.H.	Congenital bladder-neck contracture	7	Improved after surgery	6	4 ⟶ 2	Clinical status good 7 mo. after operation
S.H.	Congenital bladder-neck contracture	5	Improved after surgery	7	4 ⟶ 2	Clinical status good 7 mo. after operation
I.J.	Essential hypertension 10 yr. in duration	50	Good (7/14-7/27/55)	4	1 ⟶ 3	Sudden, unexplained deterioration; patient died on 8/20/55.
L.F.	Multiple myeloma	62	Terminal	4	4	Uremic death
B.B.	Carcinoma of prostate; ureteral obstruction.	73	Early cachexia	3	1	Slow deterioration
A.T.	Chronic glomerulonephritis	16	Terminal	4	3	Uremic death
H.R.	Chronic glomerulonephritis; anemia.	75	Cachectic	3	2	Very slow decline
J.M.	Carcinoma of bladder; ureteral obstruction.	77	Cachectic	3	2	Slow worsening in 2 mo. of observation
D.C.	Hypertension with "renal disease"	38	Unremitting edema	7	3	No response to treatment
R.L.	Essential hypertension	59	Good	4	3	Patient continues well

In this report, we underscore the preliminary, exploratory status of our disclosing an alpha-2 globulin elevation in the serum of some uremic patients. Further characterization of this component must follow from chemical analysis, such as that performed by the French workers with alpha-2 globulins in nephrotic patients[21-23] and with gamma types of abnormal globulins as studied in patients with multiple myeloma by Putnam.[15] For example, one would have to take account of comigration of lipid and protein fractions of the serum, as recently described by McDaniel and Grossman.[26] These workers incubated C^{14}-labeled fat emulsion with "heparinized" rat plasma and observed electrophoretically that some of the C^{14} activity migrated with the albumin fraction. This becomes particularly intriguing when one reviews the fundamental role of the nephrotic kidney in inducing hyperlipemia in rats, as demonstrated by Heymann and Hackel,[27] and the lipemia-clearing phenomenon as nephrosis progresses to renal failure and uremia, as investigated by Rosenman and his coworkers,[28] Anfinsen and his colleagues[29] and Nikkilä,[30] to mention but a few. Other significant biochemical and physiologic interrelations of serum alpha-2 globulins in uremia will doubtless be investigated in future appraisals.

Poli's[33] excellent and well documented article emphasized that a fundamental plasma protein configuration exists that is dynamically and effectively constant. In addition, certain proteins appear in the plasma "in transit" and are variable qualitatively and quantitatively. It is within the latter group that the alpha-globulin fraction, embodying some of the "impure" or "transit" proteins, is included. Thus, two general types of "dysproteinemias" are suggested, one of altered synthesized products and the other of abnormal waste products within the body, conveyed by the circulation for excretion or catabolism.[33] Of course, the two groups may coexist in various morbid processes. Lastly, a theoretically possible intermingling of the two groups of proteins in the plasma does not conceal their separate origins and identities, even though signs, symptoms, clinical findings and some laboratory analyses may overlap.[33]

In a final comment on the significance of alterations of serum alpha-2 globulin found in these uremic patients, the specific role of the kidney requires fur-

ther study. Whether alteration in renal function is *associated with* or *due to* extensive modification of protein metabolism remains to be explained. Whether the kidney contributes directly to the presence of abnormal or toxic catabolites in uremia is unknown. Whether the kidney is simply the "ultimate target tissue," bearing the brunt of and suffering impairment during inability to cope with the intolerable load of nitrogen catabolism in uremia-producing disease, must be elucidated.[5] Further studies must clarify the heterogeneous constituency of serum proteins in disease and, in particular, the uremic alterations of the alpha-2-globulin fraction to integrate or differentiate these from humoral, catabolic or excretory functions of the kidney.

Summary

Filter-paper electrophoresis was performed on 94 serum specimens from 47 uremic patients, of whom 44 were elderly males. By a qualitative classification (verified by quantitative photometry), unequivocally and consistently elevated alpha-2 globulin was noted in the serum of 33 of 45 patients (73 per cent of the entire group).

No direct correlation could be drawn between level of serum nonprotein nitrogen (or blood urea nitrogen), creatinine or albumin-globulin ratio and "normalcy" or elevation of alpha-2 globulin. However, in most cases, a sharply elevated serum nonprotein nitrogen and creatinine were accompanied by increased alpha-2 globulin. In determinations of total serum albumin and globulin of 20 uremic patients, 65 per cent with elevation of the alpha-2 globulin demonstrated reversal of the albumin-globulin ratio.

Functional impairment of renal parenchyma appeared to be a consistent common denominator among the diverse disease processes in which elevated serum alpha-2 globulin was detected. In at least 17 of 23 patients (74 per cent) with clinically detectable damage to renal function, serum alpha-2 globulins were clearly increased. Cardiac decompensation was the commonest extrarenal basis for elevated serum alpha-2 globulin. Of 10 patients whose uremia was observed by repeated electrophoretic tracings of the serum, the serums in 3 demonstrated a rise and fall of alpha-2 globulin in respective accompaniment with exacerbations or remissions of the clinical condition.

Primarily European publications have considered electrophoretic analyses of serum alpha-2-globulin elevations in diverse diseases, most commonly nephrosis. Such an alteration in Hodgkin's disease permitted serial observations, by electrophoresis, of clinical improvements and exacerbations. The possible value of serum protein electrophoresis as an aid in certain differential diagnoses is mentioned.

Discussion of probable sites, mechanisms and renal participation in synthesis or catabolism of abnormal serum globulins in vivo is reviewed and augmented.

We are indebted to the clinical laboratory technicians at the Veterans Administration, University of California, Southern Pacific and Franklin hospitals, all of San Francisco, for past and continuing provision of serum specimens.

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ETIOLOGIC FACTORS IN ADULT CONVULSIONS*

An Analysis of 689 Patients Whose Attacks Began after Twenty Years of Age

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BALTIMORE

THE present paper is a report on the presumptive etiologic factor in 689 patients who experienced their first major motor (grand-mal) convulsion after twenty years of age. The convulsion was generalized in 534 patients, generalized with a focal beginning in 84 and completely focal in 71. None of these patients had had any type of seizure disorder previously. *All 689 patients were examined initially by competent neurologists, neurosurgeons or internists to rule out brain tumors, metabolic disorders such as hypoglycemia and hypocalcemia or any of the acute cerebral diseases before they were referred to the Epilepsy Clinic for treatment and follow-up care.*

The ages of these patients at the time of their initial seizure ranged from twenty to seventy-two years. Five hundred and eighty-one were males, and 108 were females. Four hundred and seventy-six had had only one convulsion at the time they were first seen in the Clinic; the remaining 213 had had two or more convulsions.

The initial work-up in the Epilepsy Clinic consisted of history, physical and neurologic examination, routine test for syphilis, complete blood count and urinalysis, determinations of fasting blood sugar, calcium, phosphorus and nonprotein nitrogen and roentgenograms of the head. Electroencephalographic examinations were performed on 624 of these 689 patients. Pneumoencephalograms or cerebral arteriograms or both were obtained on 86 patients at some time during the period that they were followed in the Epilepsy Clinic. Five-hour glucose tolerance tests were performed on 15 patients in whom the initial fasting blood sugar revealed findings below 60 mg. per 100 ml.

The subsequent course of 642 of these 689 patients was studied either by regular visits to the Epilepsy Clinic or through information obtained by a follow-up questionnaire. Data, other than that obtained at the initial visit to the Epilepsy Clinic, are not available on the remaining 47 patients. One hundred and fifty-two of these 642 patients have been followed for at least five years, and the remaining 490 for ten years or longer.

Thirty-two of these 689 patients are known to be dead. Three of these deaths were accidental (drowning in 1 and injury associated with seizure in 2), and 1 was suicidal. One death was due to an intracranial neoplasm. Of the other patients death was due to neoplasm outside the central nervous system in 7, to cardiovascular disease in 8, to cerebrovascular disease in 9 and to conditions unknown but probably not neurologic in 3. Death occurred in these 32 patients within six months to twenty-five years after their first convulsive seizure.

Three of these patients died at twenty-two, twenty-six and thirty-one years of age, all from accidents. In 6 of these 32 patients death occurred between forty-four and forty-nine years of age; the remaining 23 patients died after fifty years of age. These findings are in accord with those reported previously by White, Bailey and Bickford,[1] who state that "It does not appear that seizures in themselves necessarily shorten the normal life expectancy, since the causes of death were not markedly different from the commonest causes of death listed for this country."

CYSTICERCOSIS

One patient, who was thirty-two years of age at the time of his first seizure, had roentgenographic evidence of multiple small calcified nodules in the brain. The physical and neurologic and all the usual laboratory examinations, including the electroencephalogram, were noncontributory. However, this patient lived in a community where cysticercosis infestation was prevalent at that time.

A presumptive diagnosis of cysticercosis may be ascertained by the presence of an eosinophilia, during the acute stages, the presence of palpable masses in the soft tissues and by the roentgenographic evidence of calcified areas in the brain or muscles. However, a positive diagnosis can be established only by demonstration of the parasite.

BRAIN TUMOR

Two patients had brain tumors. One was forty-five and the other forty-eight years of age at the time of the initial seizure. At this time neurologic examination was negative, and the electroencephalogram was normal in each case. The seizure was generalized in 1 patient and focal in the other. A pneumoencephalogram performed on the patient who had a focal seizure, three weeks after its occurrence, did not show abnormalities. A pneumoencephalogram was not performed on the other patient at the time of his initial work-up.

Both these patients continued to have similar seizures on the average of once or twice a month, and about nine months or so after the initial seizure

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they both presented neurologic abnormalities. Craniotomy revealed a tumor in both.

Brain Abscess

Two patients (twenty-one and twenty-eight years old at the time of their first seizure) had brain abscesses secondary to mastoid infections, which occurred at twelve and twenty-seven years of age respectively. These patients did not have convulsions at the time of the acute stages of the brain abscess. In each case the clinical seizure consisted of a focal major motor seizure on the side contralateral to the brain abscess, and the electroencephalogram revealed focal abnormalities in the area of the abscess.

Convulsions may occur both during the acute stages of a brain abscess and as a sequel of cerebral damage caused by an abscess.

Cerebral Birth Trauma

In 4 patients the initial seizures, which occurred between twenty-one and twenty-five years of age, appeared to have a direct relation to cerebral birth trauma. There was a definite history of a cerebral birth injury, with a resultant hemiplegia, in each patient. None of them had convulsions at birth.

All 4 patients had residual hemiplegic paralyses when they were seen in the Epilepsy Clinic. The convulsions were of the focal major motor type in each. The electroencephalogram revealed focal abnormalities in 3 patients and generalized abnormalities in the other. Pneumoencephalograms obtained on 2 of these patients showed considerable focal cortical atrophy and some ventricular dilatation.

Cerebral birth injuries are a frequent antecedent of epileptic convulsions. Such seizures usually appear long before the patient reaches adult life. However, since all 4 of the patients included in this study suffered focal convulsions that were limited to the hemiplegic side, it seems most likely that the convulsions were related to the cerebral damage sustained at birth.

Psychogenic Disturbances

Psychogenic disturbances were probably the most important causative factor of the seizures in 6 patients. Each of these patients had typical tonic-clonic convulsions.

Three of these patients, ranging in age from twenty-one to twenty-six years, had the first and only seizure at the time they were being examined for induction into the armed forces. These 3 patients were accepted into the service and have had no recurrence of seizures. They have been followed in the Epilepsy Clinic for at least ten years. Another patient, twenty-eight years of age, also had his first seizure at the time of his initial induction examination. He returned a week later for another examination, when he had a similar seizure. He was not accepted into the armed forces and has been followed in the Clinic for about eight years. There has been no recurrence of seizures.

Another patient, a twenty-five-year-old woman, had her first convulsion at twenty years of age. This spell occurred in a doctor's office, shortly after she had undergone a gynecologic examination before her marriage. During the subsequent five years she had four similar convulsions. These spells occurred in a doctor's office or in association with some minor injury.

Another patient, a twenty-six-year-old man, had a convulsion at twenty-two years of age. This seizure lasted approximately half an hour. It occurred when he returned to his home and found his mother, who previously had been in very good health, lying on the kitchen floor dead. The patient has been observed in the Epilepsy Clinic for approximately six years and has had no recurrence of seizures.

Electroencephalographic studies were performed on each of these 6 patients, both during the waking state and also during light, artificially produced sleep, with normal results.

One may prefer not to classify the psychogenic disturbances as the etiologic factor of convulsions in these 6 cases but merely as a precipitant of convulsions, as in some patients who have convulsive reactions in association with sudden noises, light stimulation (photogenic epilepsy) and local cutaneous stimulation (reflex epilepsy). These 6 patients may be classified as having low convulsive thresholds for adverse emotional situations.

Pregnancy

Eight patients (ranging in age from twenty-one to forty-two years) had the initial seizure in association with the first pregnancy.

In 2 of these patients the convulsions occurred during the last trimester of pregnancy. These patients presented other signs and symptoms of eclampsia. One of them has been followed for fifteen years and has had two more pregnancies without recurrence of seizures. The other patient was referred to the Epilepsy Clinic about two years after her initial seizure, which occurred in association with eclampsia. In the interim she had three more seizures that were not associated with pregnancy. Physical and neurologic examinations were negative. An electroencephalogram revealed a moderate degree of generalized abnormal slow-wave activity.

Six of these 8 patients experienced the first convulsion during the early stages of the first pregnancy. Physical, neurologic and all the usual laboratory examinations, including the electroencephalogram, were noncontributory. Two of these 6 patients had a recurrence of similar convulsions during the early stages

of other pregnancies; 2 had subsequent pregnancies without a recurrence of seizures; and 2 have not been pregnant again and also have not had a recurrence of seizures.

It is well known that convulsions occur in association with eclampsia and also that epilepsy subsequently develops in some patients who have eclampsia. However, it is difficult to explain the occurrence of convulsions in the 6 patients who had them only during the early stages of their pregnancies. These patients did not have hypertension at that time. They may have a low convulsive threshold, and the stresses and strains of pregnancy or some metabolic changes that occurred during pregnancy may have triggered off the seizures. On the other hand it may be that these 6 patients should be classified as having cryptogenic epilepsy, which coincidentally appeared at the time of pregnancy.

Neurosyphilis

Eleven patients had convulsions in association with the secondary or tertiary stage of syphilis. These patients were seen initially about thirty years ago, when syphilis of the central nervous system was a frequent cause of seizures that developed in adult life. Walker,[2] in a paper presented twenty years ago, lists syphilis as the etiologic factor for convulsions in 15 of 100 adults. Owing to the early diagnosis and more adequate treatment of syphilis in its earlier stages, one rarely sees this type of convulsion today.

Post-Traumatic Convulsions

By post-traumatic convulsion is meant a convulsion resulting from cerebral trauma occurring at times other than at birth.

In 17 patients, ranging in age from twenty-one to forty-nine years, the seizures appeared to have a direct relation to cerebral trauma. In 12 of these 17 patients the trauma consisted of closed head injuries that were followed by unconsciousness lasting for one to six hours; in the other 5 the injuries were open wounds of the head.

The initial seizure occurred within six months of the head injury in 6 patients and one to five years after the injury in the other 11.

In 14 of these 17 patients both the clinical seizures and the electroencephalograms presented focal characteristics. In the other 3, the seizures were generalized, and the electroencephalogram revealed focal abnormalities in 1 and generalized abnormalities in another and was normal in the other. Pneumoencephalograms, obtained on 4 of these 17 patients, showed focal cortical atrophy and ventricular dilatation in 3 and were normal in the other.

The occurrence of convulsions in patients who previously had sustained cerebral trauma is sometimes difficult to evaluate and frequently becomes an important medicolegal problem, particularly when the seizures occur many years after the head injury. Seizures that follow brain trauma are commonly classified as secondary (or organic) epilepsy. However, one must admit that in many cases it is impossible to be certain about the traumatic etiology since many persons who sustain similar head injuries never have convulsions. It may be that other, nondemonstrable factors are responsible for the seizures in such cases.

Walker[3] makes the following comment:

> . . . the convulsions in posttraumatic epilepsy usually begin within two years of the cerebral injury; if a longer latent period exists, the possibility of some other etiological factor is enhanced. The traumatic etiology in such late developing cases of epilepsy must be established from the clinical history and findings, the electroencephalographic and pneumoencephalographic alterations and by elimination of other possible cause.

Stevenson[4] reports that the frequency of post-traumatic epilepsy appears greater the longer the period in which the cases are followed, for many patients do not have seizures for five to fifteen years after a head injury.

The following factors favor a relation between convulsions and cerebral trauma: when the seizures occur soon after the brain injury — that is, within one year or so; when the clinical seizure or the electroencephalogram or both present focal characteristics; and when there is pneumoencephalographic evidence of some cerebral abnormality, especially in the region of the head injury. However, it must be noted that sometimes one sees focal clinical seizures or focal electroencephalographic abnormalities, or both, in patients with convulsive disorders in whom there is no history or demonstrable evidence of brain damage. Walker[3] states, "In posttraumatic epilepsy, the seizure, although eventually generalized, has in approximately 80 per cent of cases focal manifestations, whereas the incidence of a local beginning in idiopathic epilepsy is approximately one-half of this figure."

Alcohol

Twenty-eight patients had seizures in association with excessive use of alcohol.

In 22 of these the initial convulsion occurred on the day after an alcoholic debauch. In the other 6 the initial seizure occurred while the patients were still in a state of alcoholic intoxication. None of these 28 patients had seizures at any time except in association with the excessive use of alcoholic beverages.

Fifteen of these 28 patients had a recurrence of similar convulsions under similar circumstances. There has been no recurrence of seizures in the other 13 patients, after a complete abstinence from alcohol.

Pneumoencephalograms were obtained on 3 of these 28 patients and were normal in each. A routine electroencephalogram was normal in all 28 patients.

The occurrence of seizures after an alcoholic de-

bauch is probably related to the abrupt withdrawal of alcohol. A similar withdrawal phenomenon is sometimes seen in association with a sudden withdrawal of barbiturates. Ford[5] states that convulsions occurring during alcoholic intoxication are occasionally due to hypoglycemia. He believes that this applies to the use of "smoke" especially.

Hypertension and Arteriosclerosis

Eighty-three patients, ranging in age from forty to seventy-two years, revealed the following physical findings at the time of their first convulsion: hypertension, with systolic readings above 200 in 23 cases; peripheral arteriosclerosis, which might be accepted as presumptive evidence of vascular changes in the brain in this age group, in 11; both sclerosis of the vessels and hypertension in 42; and focal brain damage, presumably on a vascular basis, in 7.

The initial clinical seizure was focal in the 7 patients who presented focal brain damage and also in 5 of the others and was generalized in the remaining 71. Pneumoencephalographic studies on 11 of these 83 patients had the following results: in 2 patients with hypertension alone it was normal; in 3 patients with hypertension and arteriosclerosis, it was normal in 1 and gave evidence of generalized cortical atrophy in 2; in 3 patients with focal brain damage, it revealed focal cortical atrophy in 2 and generalized atrophy in 1; in 3 patients with arteriosclerosis alone, it showed generalized cortical atrophy in 2 and was normal in 1. The electroencephalogram revealed abnormalities in 65 (78 per cent) of these 83 patients, and was normal in the remaining 18.

A good deal has been written on the role of hypertension and arteriosclerosis in the production of epilepsy.[1,6-16] It is believed that cerebral anemia, caused either by vasoconstriction or narrowing of the lumen of a vessel by arteriosclerosis, is probably one of the most important factors in the production of epileptic attacks in these disturbances. Ford[5] believes that some of the middle-aged and elderly patients who have seizures must be suffering from one of the presenile dementias. However, he admits that only rarely does one have the opportunity to demonstrate such conditions.

Cryptogenic (or Idiopathic) Epilepsy

With the diagnostic procedures employed in the Epilepsy Clinic, a specific etiologic factor was not discoverable in 527 (78 per cent) of the 689 patients included in this study. A hundred and three of these 527 patients have been followed for at least five years, and 409 for ten years or longer. Data besides those obtained at the initial visit to the Clinic are not available on the remaining 15 patients.

The initial clinical seizure was generalized in 454 patients, generalized with a focal beginning in 41 and completely focal in 32. Routine twenty-minute electroencephalograms obtained on 501 of these 527 patients revealed abnormalities in 335 (67 per cent) and were normal in the remaining 166. Pneumoencephalographic studies were performed on 54 of these 527 patients and were normal in each.

It must be emphasized that a diagnosis of cryptogenic epilepsy should be made only when every possible etiologic factor has been eliminated. Even then a careful watch is necessary for any further developments that might indicate that an organic cause has been overlooked. It seems quite obvious that all types of epilepsy must be due to some type of anatomic or physiologic cerebral defect.

Discussion

The results of this follow-up study of 689 patients and also those of several other workers[2,17,18] show that convulsions without demonstrable cause (cryptogenic or idiopathic epilepsy) developing for the first time in adulthood are relatively common. This finding is contrary to the attitude of many physicians in the past, and even of some today, who consider that convulsions appearing for the first time in adults are usually symptoms of some serious underlying cerebral disturbance with grave prognostic implications.

Five hundred and twenty-seven (78 per cent) of the 689 patients included in this study are classified as having cryptogenic (idiopathic) epilepsy. All but 15 of these patients have been followed for a prolonged period — the majority for ten years or longer. The passage of time almost definitely rules out the likelihood of an intracranial neoplasm or some cerebral degenerative disturbance in these cases. Pneumoencephalograms were obtained on 54 of these 527 patients at some time during the first years after the initial seizure and were normal in each case. It is realized, however, that if pneumoencephalograms or cerebral arteriograms or both had been obtained on all 527 patients, abnormalities might have been revealed in some. In such cases a possible cause for the convulsions would have been demonstrated, and obviously these patients would no longer be regarded as having cryptogenic epilepsy. It is also possible that some of the 527 patients classified as having cryptogenic epilepsy sustained cerebral trauma that was not recognized by the patient and not detectable with the diagnostic procedures employed in the Clinic.

The second most common presumptive cause for convulsions in this group of 689 patients was hypertension or cerebral arteriosclerosis. *However, it should be emphasized that hypertension or arteriosclerosis should be considered only as a presumptive cause for convulsions.* Regardless of the presence of either or both of these disturbances, each patient should be examined extensively for all possible causes for seizures. For example, 1 patient, not included in this study, a fifty-year-old woman, was referred to the Epilepsy Clinic with a diagnosis of "convulsions due to a

hypertensive encephalopathy." She had had severe hypertension (systolic readings of over 240) for three years or so and had been having major motor (both focal and generalized) seizures once or twice a month for about six months before her visit to the Clinic. Except for the hypertension, the physical and neurologic examinations were negative. After admission to the Clinic a routine roentgenogram of the skull revealed a large calcified area within the cerebral cortex. A craniotomy was performed, and a large meningioma was removed. This patient has continued to have severe hypertension but has had no recurrence of seizures for about nine months.

It is of interest that 581 (80 per cent) of the 689 patients included in this study were males. This sex difference in age at onset of epilepsy in adults was noted by Gowers[19] in 1901. He reported that under thirty years of age the frequency of onset of seizures was higher in females and that after thirty years of age the relation of sex to age at onset was reversed and the rate of occurrence was higher among males. After thirty years of age the excess of males was 29 per cent, and after sixty years of age males suffered almost exclusively. White, Bailey and Bickford[1] also reported that a preponderance of males were afflicted in their group of 107 patients whose seizures began after the age of fifty years. This difference in sex distribution in the later years of life — that is, after fifty years — may be explained by the fact that males generally are more prone to arteriosclerosis than females. Eighty-seven of the 105 patients in our series whose convulsions occurred for the first time after fifty years of age were males. Another possible explanation is that men are more susceptible to head injuries since they generally lead a more active life than women. Penfield and Jasper[16] state, "Attacks which begin after 18 or 20 years of age, and before 35, are most often caused by head trauma or by intracranial neoplasm, the former being the most frequent cause." The findings of this present study and also those of several other workers[2,17,18] are not in accord with that statement. It may be that Penfield and Jasper see a very weighted group of patients and also that their criteria for diagnosing cerebral trauma are different from those employed in this study.

Because of the serious implications of seizures developing for the first time in adults, it is important that diagnostic methods be sufficiently complete to indicate the presence or absence of an intracranial neoplasm and that these procedures be put in proper perspective so far as their usefulness and benignancy are concerned. It has been reported that 25 to 45 per cent of patients with brain tumors have seizures[20-22] and that about 15 to 40 per cent have seizures as the initial symptom.[16,23-26]

It is my belief that the generalization that every adult in whom a seizure disorder develops should be subjected to pneumoencephalography or cerebral arteriography or both should be questioned. When one considers the risk and expense involved in the performance of these examinations, one does not have much, if anything, to lose by performing these tests on a selective basis. By and large the major reason for the performance of these procedures in patients suffering with convulsive disorders is to determine the presence or absence of a space-occupying lesion. Of course, it must be remembered that a normal pneumoencephalogram does not preclude the presence of a tumor.[27-32]

I believe that the following findings should be considered indications for immediate pneumoencephalography or cerebral arteriography or both: when there are positive neurologic abnormalities, other than those explained by previous brain damage, such as hemiplegias from cerebral birth trauma (most patients who have a convulsion as a presenting symptom of a brain tumor will manifest sufficient neurologic abnormalities for a correct diagnosis to be made at that time); when there are signs or symptoms of increased intracranial pressure (in such cases ventriculography should be performed and spinal encephalography is usually contraindicated); when the clinical seizures are focal; and when there are focal abnormalities in the electroencephalogram.

Pneumoencephalography or cerebral arteriography need not be included in the initial work-up of a patient at the time of his first convulsion or even subsequent convulsions when the clinical seizure is generalized, the neurologic, including a thorough funduscopic, examination is negative and the electroencephalogram reveals generalized abnormalities or is normal. However, pneumoencephalography should be considered if findings such as those mentioned above subsequently become apparent. One also should consider pneumoencephalography in all cases in which there is any doubt about the co-operation of the patient or the availability of competent follow-up care and in patients in whom the seizures recur in spite of proper medical therapy. The reason for the performance of this test in such cases is twofold: to investigate the possibility of an intracranial neoplasm and to determine the presence of other abnormalities that may make the patient a candidate for elective epileptic surgery.

Summary and Conclusions

Data are presented showing that convulsions, without discoverable cause or evidence of organic brain disease, occurring for the first time in adulthood are relatively common. Five hundred and twenty-seven (78 per cent) of 689 patients, ranging in age from twenty to seventy-two years, are classified as having cryptogenic (or idiopathic) epilepsy. Other presumptive causes for convulsions were cysticercosis, brain tumor, brain abscess, cerebral birth trauma, psychogenic factors, pregnancy, neurosyphilis, post-

traumatic (cerebral) conditions, alcohol, hypertension and arteriosclerosis.

It should be emphasized that the 689 adults included in this study constitute a weighted group of patients and that the number of the various presumptive etiologic factors reported is by no means representative of convulsive disorders in the general adult population. *All these 689 patients were examined initially by competent neurologists, neurosurgeons or internists to rule out brain tumors, metabolic disorders such as hypoglycemia and hypocalcemia or any of the acute cerebral diseases before they were referred to the Epilepsy Clinic for treatment and follow-up care.*

It should be noted also that there are many etiologic factors for convulsions in adults other than those reported in the present study.

It should be emphasized that cryptogenic (cause not discoverable) epilepsy or any of the other presumptive causes for convulsions mentioned in this present report should be considered only when every possible etiologic factor has been eliminated. *Every patient suffering with a convulsive disorder should be examined exhaustively to rule out serious organic lesions such as brain tumors.*

The indications for pneumoencephalography or cerebral arteriography or both are presented.

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STEROID THERAPY OF HYPERCALCEMIA AND RENAL INSUFFICIENCY IN SARCOIDOSIS*

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THE damaging effect on the kidney of uncontrolled hypercalcemia leading to nephrocalcinosis and renal insufficiency seems well established.[1-3] One of the diseases with which hypercalcemia is at times associated is Boeck's sarcoid. Several articles in the past two years indicate that steroid therapy can correct this disturbance of mineral metabolism when it occurs in sarcoidosis.[4-7] We wish to describe our experiences in the successful treatment of hypercalcemia in 2 patients with sarcoidosis and to point out subsequent improvement in renal function. The apparent uniform success of steroid therapy for hypercalcemia of this type deserves emphasis since its continuation unrecognized or untreated may lead to irreversible damage to the kidney and uremia.

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Case Reports

Case 1 (V.A.H. 12727). A 28-year-old man had fever, migratory joint pain and red, nodular lesions of the skin of the anterior surface of both lower legs in 1950. A film of the chest at that time showed fine stippling of both lung fields and bilateral hilar adenopathy. A skin test with tuberculin was mildly positive with the use of purified protein derivative 2d strength. A tentative diagnosis of sarcoid was

made. He was next seen in 1952 because of anorexia, fatigue and a weight loss of 15.9 kg. (35 pounds). Shiny, erythematous, papular skin lesions had developed on the trunk and arms. Biopsy of one of these and of a random specimen of gastrocnemius muscle showed granulomas consistent with sarcoid. An x-ray film of the chest again was abnormal, with a fine stippling in both lung fields and hilar shadows consistent with enlarged lymph nodes. Films of the hands were normal. A blood count was normal; the urine gave a + test for protein, with a rare red cell and white cell per high-power field and an occasional hyaline cast in the sediment. Renal-function tests revealed a maximum specific gravity of the urine of 1.010. A phenolsulfonphthalein test showed 3 per cent excretion of the dye in the 1st 15 minutes and a total of 25 per cent in 2 hours. The blood urea nitrogen was 11 mg. per 100 ml. On an intravenous pyelogram no dye was visualized in the kidney areas. Other laboratory data included persistent ++++ tests in the urine for calcium with the use of the Sulkowitch reagent. A serum calcium of 14.4 mg., a serum inorganic phosphorus of 3.4 mg., a serum alkaline phosphatase of 4.3 Bodansky units, a serum albumin of 3.5 gm. and a serum globulin of 2.5 gm. per 100 ml. Repeat serum calcium levels were again found to be abnormally high, being 13.8 and 14.0 mg. per 100 ml.

In the hospital anorexia and weakness persisted, as did the evidence of disturbed calcium metabolism by chemical determination. Since steroid therapy had been shown at times to influence the lesions of sarcoid favorably it was decided to treat this patient with cortisone, although at that time (October, 1952) the effect of such therapy on the hypercalcemia of sarcoid had not been reported. He was given cortisone, 100 mg. daily for a period of 14 days. The serum calcium promptly fell to normal levels within 5 days, and the urine Sulkowitch test declined from ++++ to + at the same time. X-ray study of the chest remained unchanged, but in a matter of days the skin lesions disappeared, the appetite returned, and the patient became asymptomatic.* He was seen periodically at follow-up examinations over the next 2½ years, during which he remained symptom free and had gained 9.1 kg. (20 pounds) in weight. The serum calcium remained normal without further steroid therapy.

Renal function was re-evaluated 3 months after treatment with cortisone, when minimal improvement was found. The maximum specific gravity had increased from 1.010 to 1.012; phenolsulfonphthalein excretion was 7 per cent in the 1st 15 minutes and 28 per cent in 2 hours, compared with 3 per cent in 15 minutes and 25 per cent in 2 hours before cortisone therapy. However, retesting 2½ years after cortisone correction of the hypercalcemia showed that tests of renal function had improved significantly, to almost normal levels. The maximum specific gravity at that time was 1.020; phenolsulfonphthalein excretion was 25 per cent in the 1st 15 minutes and a total of 61 per cent in 2 hours (Table 1). The urinary sediment had completely cleared, and no protein was present.

The following points seem worthy of note in this case of sarcoid with hypercalcemia:

The elevated serum calcium promptly fell to normal during the fourteen days of cortisone therapy.

Hypercalcemia has not recurred during the two and a half years of follow-up study, although no further steroid medication has been administered.

Renal insufficiency was present before treatment during the period of uncontrolled hypercalcemia. After cortisone treatment improvement in renal function was minimal after three months, but at the end of two and a half years reversal of renal insufficiency had occurred, with return to nearly normal levels of function.

*This initial response to cortisone was described in a previous report in this journal.[7]

Case 2 (V.A.H. 32070). A 48-year-old man was first studied in 1950, when generalized lymphadenopathy, hepatosplenomegaly and abnormal hilar and paratracheal densities were noted on x-ray study of the chest. Biopsies of a supraclavicular lymph node and a random section of gastrocnemius muscle showed granulomas consistent with Boeck's sarcoid. He re-entered the hospital in September, 1955, because of vomiting, polyuria, generalized weakness and weight loss that began 3 weeks previously. Physical examination revealed a well developed and fairly well nourished man. The blood pressure was 160/80. Other findings included enlargement of the liver, which extended to 4 cm. below the right costal margin in the midclavicular line, enlargement of the spleen, which was palpated 4 cm. below the left costal margin on inspiration, a palpable lymph node about 1 cm. in diameter in the right axilla and a node about 2 cm. in size in the left inguinal region. Muscle strength seemed normal, and deep tendon reflexes were present and equal.

A hemogram was normal. The urine contained a trace of albumin, with 2 red cells and occasional white cells per high-power field in the sediment. The blood urea nitrogen was 29 mg. per 100 ml. The maximum specific gravity of the urine was 1.010 by the Fishberg concentration test. Phenolsulfonphthalein excretion was 13 per cent in the 1st 15 minutes and 38 per cent in 2 hours. The serum inorganic phosphorus was 3.2 mg., the serum alkaline phosphatase 3.6 Bodansky units, the serum albumin 4.9 gm., and the serum globulin 2.0 gm. per 100 ml. Several serum calcium determinations on different days revealed levels of 13.0 mg., 13.6 mg., 13.0 mg. and 13.6 mg. per 100 ml. The urinary Sulkowitch test was consistently ++++.

X-ray studies showed the chest film unchanged from 1950, with persisting abnormal hilar and paratracheal densities considered to be enlarged lymph nodes. An upper gastrointestinal series was normal. An intravenous pyelogram gave fair visualization of dye in the excretory urinary tract. The left kidney appeared to have a convex defect on the lateral aspect interpreted as pressure from the enlarged spleen. This was confirmed by retrograde pyclography. No other abnormalities were noted.

Gastric aspiration revealed 20 ml. of residual fluid. On symptomatic treatment the vomiting subsided. Because of the clear evidence of hypercalcemia and renal insufficiency it was decided to treat the patient with steroid therapy. He was given prednisone (Meticorten) for a period of 14 days, receiving 30 mg. daily for 9 days and then 40 mg. daily for the last 5 days. The urinary Sulkowitch test remained ++++, and no reduction in the serum calcium occurred. Cortisone, 300 mg. daily, was then begun and was continued for a total of 11 days. By the 4th day of cortisone treatment the serum calcium had decreased to 11.5 mg. and by the 8th day it was 9.3 mg. per 100 ml. The serum phosphorus fell to 2.3 mg. per 100 ml. No further steroid therapy was administered. Follow-up determinations of the serum calcium 45 and 74 days after cortisone had been discontinued showed them to remain within normal limits. The urinary Sulkowitch test decreased to + coincident with the decrease in serum calcium. Renal function showed significant improvement by 45 days and had returned to nearly normal 74 days after correction of the hypercalcemic state with cortisone (Table 2). The maximum specific gravity increased from 1.010 to 1.022; phenolsulfonphthalein excretion rose from 13 to 25 per cent in the 1st 15 minutes, and the blood urea nitrogen declined from 29 mg. to 21 mg. per 100 ml.

The following points seem worthy of note in this case of hypercalcemia due to sarcoid:

Prednisone in average doses over a fourteen-day period failed to influence the elevated serum calcium level or the urinary Sulkowitch test.

Therapy with cortisone, however, was followed by a prompt fall of the abnormally high serum calcium levels to normal.

Hypercalcemia did not recur during the seventy-four days of follow-up study, although no further

steroid medication was administered. This is admittedly not a prolonged period of observation; nevertheless, no immediate "rebound" occurred in the serum calcium when cortisone was omitted.

Renal function showed significant improvement within forty-five days and had returned to nearly normal in seventy-four days.

Discussion

Hypercalcemia has been reported as occurring in between 20 and 45 per cent of cases of sarcoid.[8] The presence of this disturbance of mineral metabolism in sarcoidosis may be suggested by the development of symptoms referable to hypercalcemia per se. These include lack of muscle tone, with weakness, constipation, anorexia, vomiting and visual difficulties. Polyuria may occur because of excretion of large amounts of calcium. Symptoms from renal complications include renal colic due to calculi and, in advanced cases, symptoms secondary to renal insufficiency, the result of damage by calculi or nephrocalcinosis.

The biochemical features of this disorder of mineral metabolism in sarcoid are elevation of the serum calcium, and a marked increase in urinary calcium excretion.[9] The serum inorganic phosphorus is normal or elevated. The serum alkaline phosphatase is normal. No correlation has been found between hypercalcemia and the bone lesions seen in sarcoid and elevation in the serum globulin sometimes present in the disease.[8,9]

In the differential diagnosis one must exclude other causes of hypercalcemia. These are usually enumerated as follows: hyperparathyroidism; syndrome of ingestion of milk and alkali (Burnett's syndrome); acute osteoporosis; multiple myeloma; metastatic cancer; and vitamin D intoxication. The fact that some of these entities are also characterized by bone lesions and dysproteinemia increases their superficial resemblance to sarcoid. It is beyond the scope of this paper to enter into a detailed discussion of the enumerated conditions, but certain distinguishing features are noted. These are most helpful when a tissue diagnosis consistent with sarcoid is not at the moment available.

Hyperparathyroidism is usually excluded by the tendency for the serum inorganic phosphorus to decrease rather than to be increased as in sarcoid.[10] The prompt return to normal of the serum calcium with steroid therapy in sarcoid has been mentioned as another differential point.[5] Bone disease in sarcoid, if present, tends to be localized whereas that seen in hyperparathyroidism is generalized.[9] Certain clinical features such as lymphadenopathy, uveitis, skin lesions and hepatosplenomegaly suggest the diagnosis of sarcoid, but their presence is variable.[8]

The other entities may mimic the biochemical abnormalities of sarcoid in that there is elevation of the serum calcium and inorganic phosphorus, but differentiation is usually possible. In Burnett's syndrome there is a history of prolonged excessive intake of milk and alkali. The urinary excretion of calcium tends to be low rather than increased as in sarcoid.[11] The biochemical abnormalities in acute osteoporosis depend on immobilization of the patient under conditions of very active bone formation temporarily liberating from this tissue larger amounts of calcium phosphate than can be handled by the kidney.[14] Metastatic carcinoma is distinguished by the finding of a primary tumor. In addition, the x-ray picture of the bone lesions does not as a rule suggest sarcoid. Myeloma may reveal hyperglobulinemia in addition to bone lesions. However, the characteristics of the electrophoretic curve,[13] absence of serum antibodies,[14] presence of Bence-Jones protein and plasma-cell infiltration in the marrow are helpful distinguishing features. Vitamin D intoxication is usually diagnosed by a history of ingestion of this substance. However, the patient with sarcoid or one of the other conditions noted may have had vitamin therapy so that a history of vitamin D intake does not necessarily

Table 1. *Course in Case 1.*

Date	Serum Calcium	Blood Urea Nitrogen	Serum Alkaline Phosphatase	Serum Phosphorus	Maximum Specific Gravity of Urine	Phenolsulfonphthalein Excretion		Cortisone Administration
						in 15 min.	in 120 min.	
	mg./100 ml.	*mg./100 ml.*	*units*	*mg./100 ml.*		%	%	*mg./day*
10/7/52	14.5	11	4.3	3.4	1.010	3	25.0	100*
10/21/52	9.4	—	—	2.8	—	—	—	100*
Nov., 1952	9.5	11	3.4	2.8	1.012	—	—	—
Jan., 1953	9.3	14	2.7	3.4	1.012	7	28.0	—
June, 1953	9.6	12	3.2	3.0	1.015	—	—	—
Jan., 1954	9.6	16	3.0	2.8	1.015	—	—	—
June, 1954	9.9	—	—	3.0	1.018	—	—	—
Jan., 1955	10.0	15	—	3.0	1.020	25	61.5	—

*Given for 14 days between dates indicated.

exclude other entities. It is of note that patients with sarcoid are very sensitive to vitamin D,[15] a fact that is commented on below.

It is probable that the problem usually does not revolve about an exercise on the differential diagnosis of hypercalcemia, but rather failure of investigation for the presence of disordered calcium metabolism in the patient with sarcoidosis. Since the correction of this dangerous state is possible by proper treatment, more attention should be paid to this complicating disorder of metabolism, rather than the interesting and time-honored abnormality of serum protein, if laboratory study is limited by financial factors. The simplest, most economical method of follow-up study is urinary calcium determination by the Sulkowitch test. Frequent + + + + tests indicate the need for subsequent serum calcium determinations. This is especially true if the high level of urinary calcium persists when milk is eliminated from the diet.

The mechanism of hypercalcemia in sarcoid has recently been clarified.[5,18] Greater than normal absorption of calcium and phosphorus from the gastrointestinal tract has been demonstrated in cases with hypercalcemia. A low level of fecal calcium has been found. Reduction in the abnormally high level of serum calcium has resulted during administration of a low-calcium diet.[5] Production of a substance like vitamin D has been postulated in sarcoidosis. The high urinary level of calcium excretion, which may exceed the dietary intake, has been considered to be related to the parathyroid-hormone-like action of vitamin D, resulting in a tendency to increased urinary phosphorus excretion, loss of serum phosphorus, unsaturation of the serum calcium phosphate, demineralization of bone, increase in serum calcium and thus increased loss of calcium in the urine.[16]

The etiology of renal failure in sarcoid has been found to be related to multiple causes. In most cases it has been associated with nephrocalcinosis.[8,17] Other diseases such as renal tuberculosis and pyelonephritis are present in some cases at autopsy.[8,17] Involvement of the kidney with the sarcoid granuloma is not uncommon, but the lesions are usually few in number and scattered so that their role in the production of renal insufficiency has been doubted.[8] Recently, a case of massive sarcoid involvement of the kidney, and renal insufficiency without hypercalcemia or nephrocalcinosis, has been reported in which the renal failure was attributed to the granulomatous involvement.[17]

There thus seem to be three well documented types of lesions that might account for renal failure in a given case of sarcoid — namely, nephrocalcinosis secondary to hypercalcemia, involvement of the kidney with other pathologic processes and massive infiltration with granulomas of sarcoid per se. The possibility of a fourth type of renal insufficiency is suggested by certain findings that have been noted. These involve patients in whom steroid treatment of hypercalcemia was associated with a rapid improvement in renal function over a period of several days. Such a patient (No. 4 in Table 3), described by Dent et al.,[4] was a twenty-three-year-old man with sarcoid and a serum calcium level of 14.3 mg. per 100 ml. Renal insufficiency was present. After cortisone therapy for twenty-three days the serum calcium became normal. Renal function improved greatly during the treatment period, the blood urea nitrogen decreasing from 60 mg. to 24 mg. per 100 ml., urea clearance increasing from 47 to 75 per cent of normal, and the specific gravity of the urine rising from 1.010 to 1.020. A month later biopsy of a kidney was done during surgical removal of a renal

TABLE 2. *Course in Case 2.*

DATE	SERUM CALCIUM	URINARY CALCIUM*	BLOOD UREA NITROGEN	SERUM ALKALINE PHOSPHATASE	SERUM PHOSPHORUS	MAXIMUM SPECIFIC GRAVITY OF URINE	PHENOLSULFONPHTHALEIN EXCRETION		CORTISONE ADMINISTRATION
							IN 15 MIN.	IN 120 MIN.	
	mg./100 ml.		*mg./100 ml.*	*units*	*mg./100 ml.*		%	%	*mg./day*
9/20/55	13.0	+ + + +	29	3.6	3.2	1.010	13.0	38	—
10/18/55	13.2	+ + + +	—	—	3.6	—	—	—	300†
10/21/55	11.5	+	—	—	2.1	—	—	—	300
10/25/55	9.3	+	—	—	1.8	—	—	—	300
10/28/55	9.3	+	27	—	2.3	—	8.0	45	300†
11/1/55	10.1	+	—	—	3.6	1.026	—	—	—
11/8/55	9.3	+	—	—	2.9	—	—	—	—
11/15/55	10.5	+ +	—	—	2.7	—	17.0	53	—
12/13/55	10.1	+	21	—	2.7	1.022	18.4	47	—
1/13/56	11.0	+	21	—	4.0	1.022	25.5	61	—

*Sulkowitch test.
†Given for 11 days between dates indicated.

calculus. The biopsy section showed mild pyelonephritis without evidence of nephrocalcinosis or sarcoid granuloma. Other reported cases (No. 1 and 7 in Table 4)[6,5] tended to show improvement in renal function during therapy with steroids. In Case 2, reported above (Case 10 in Table 4), evidence of improvement in renal function occurred within forty-five days of correction of the hypercalcemic state with cortisone. The blood urea nitrogen fell from 29 mg. to 21 mg. per 100 ml. Phenolsulfonphthalein excretion increased from 13 to 18 per cent in the first fifteen minutes, and the maximum specific gravity from 1.010 to 1.020. After seventy-four days the phenolsulfonphthalein excretion had risen to 25.5 per cent in the first fifteen minutes, and the specific gravity to 1.022. In patients whose improvement in renal function is slow and gradual after the correction of the hypercalcemia state (Table 1) it is likely that nephrocalcinosis is the underlying renal lesion. However, in those whose renal function improves during or soon after steroid therapy, the rapidity of change does not seem consistent with disappearance of nephrocalcinosis. Clarification of the mechanism of improvement awaits further renal-biopsy studies before and after steroid therapy. Some other possible explanations besides disappearance of nephrocalcinosis have already been mentioned. The first is that there was massive granulomatous involvement of the kidney that improved during steroid therapy. Against this concept is the apparent rarity of massive sarcoidosis of the kidney and absence of granuloma in the renal biopsy taken in the case reported by Dent et al.[4] (Case 4, Table 3). Since this biopsy specimen was taken after therapy with steroids had been carried out, complete clearing of pre-existing lesions of sarcoid cannot be excluded. Secondly, it is possible that other types of renal disease were present and improved with steroid therapy. There is no evidence to support this concept. Another possibility is that steroid therapy had a favorable, nonspecific effect on renal function. It has been shown that steroids result in increased glomerular filtration rate in normal persons.[18] It is difficult, however, to see how such a beneficial effect would persist or explain the continued improved state of renal function after therapy has been discontinued. Lastly, it has been suggested that hypercalcemia per se may cause renal impairment.[12,19] A functional type of renal insufficiency occurs in other disordered metabolic states.[20] That excessive calcium content of the renal tubular cells or calcium phosphate tubular casts interfere with normal function even before clinically detectable nephrocalcinosis has developed may be speculative, but improvement of kidney function in certain cases

TABLE 3. *Response of Serum Calcium to Steroids.*

SOURCE OF DATA	CASE NO.	BEFORE TREATMENT		TYPE OF TREATMENT	DURATION	AFTER TREATMENT		EFFECT ON SERUM CALCIUM	SUBSEQUENT COURSE
		SERUM CALCIUM	SERUM PHOSPHORUS			SERUM CALCIUM	SERUM PHOSPHORUS		
		mg./100 ml.	*mg./100 ml.*		*days*	*mg./100 ml.*	*mg./100 ml.*		
Shulman et al.[6]	1a	15.8	5.1	ACTH	7	9.8	3.7	Normal in 5 days	Patient re-treated after 8 mo. (see 1b)
	1b	13.8		Cortisone	14	10.9		Normal in 14 days	Remained normal during 18-mo. follow-up study
	2	16.9	3.8	ACTH	11	10.7	3.1	Normal in 11 days	Patient remained well during 18-mo. follow-up study
	3	12.5		ACTH	9	9.0		Normal in 12 days	Patient died with nephrocalcinosis 1 wk. later
Dent et al.[4]	4a	14.3	4.2	Cortisone	23	10.1	2.2	Normal in 13 days	Patient re-treated after 24 mo. (see 4b)
	4b	15.2		Cortisone		Normal		Normal in 20 days	Patient kept on maintenance cortisone; serum calcium normal during 1-yr. follow-up study.
Anderson et al.[5]	5	13.2		Cortisone	15	10.0		Normal in 10 days	Data inadequate
	6	13.5		Cortisone		11.2		Fall by 20th day	Patient kept on maintenance cortisone & low-calcium diet; duration not given.
	7	14.0		Cortisone		10.4		Normal in 20 days	Patient kept on maintenance cortisone; serum calcium remained normal during 10-mo. follow-up study.
Henneman et al.[36]	8			Cortisone				Fall	Further data not given
Phillips[7]	9	14.5	3.4	Cortisone	14	9.4	2.8	Normal in 14 days	Serum calcium remained normal during 27-mo. follow-up study
Present report (Case 2)	10	13.0	3.8	Cortisone	11	9.3	2.1	Normal in 8 days	Serum calcium remained normal during 74-day follow-up study

seems associated with a fall in serum calcium to normal levels.

The results of treatment of hypercalcemia in sarcoid with steroids is summarized in Tables 3 and 4. A total of 8 cases were found in the literature, to which we have added two more. The following points seem worthy of note:

The subsequent course as measured by the level of serum calcium was variable. Immediate rebound to high levels upon cessation of therapy did not occur, although in 2 cases the hypercalcemic state recurred some time later. Retreatment with steroids was again successful in reducing the elevated serum calcium to normal. In 3 patients, the

TABLE 4. *Effect of Correction of Hypercalcemia on Renal Function.*

Source of Data	Case No.	Before Treatment				Type of Treatment	Duration of Treatment	After Treatment				Rapidity of Change	Subsequent Course
		Specific Gravity	Phenolsulfonphthalein Excretion		Nonprotein Nitrogen	Blood Urea Nitrogen		Specific Gravity	Phenolsulfonphthalein Excretion		Nonprotein Nitrogen	Blood Urea Nitrogen	
			% in 120 min.	% in 15 min.	mg./100 ml.	mg./100 ml.	days		% in 120 min.	% in 15 min.	mg./100 ml.	mg./100 ml.	
Shulman et al.[6]	1	1.021	20.0	—	57	—	ACTH 7	1.018	20.0	—	41	—	14 days	Patient re-treated 3 times, with improvement in renal function each time
	2	—	20.0	—	56	—	ACTH 11	—	20.0	—	56	—	(Unchanged)	Patient asymptomatic for 18 mo.; no other data.
	3	—	17.5	—	134	—	ACTH 9	—	—	—	180	—	9 days	Patient died of nephrocalcinosis 1 wk. after discharge
Dent et al.[4]	4	1.010	—	—	—	60	Cortisone 23	1.014	—	—	—	24	23 days	Improvement maintained during 2 mo. follow-up study
Anderson et al.[5]	5a	—	—	—	—	175	Cortisone 5	—	—	—	—	90	5 days	Patient re-treated after 14 mo. (see 5b)
	5b	—	—	—	—	114	Cortisone —	—	—	—	—	126	(Unchanged)	No improvement on maintenance therapy
	6	—	—	—	—	40	Cortisone —	—	—	—	—	"Normal"	(Data not given	Blood urea nitrogen said to be normal 17 mo. later
	7	—	—	—	—	162	Cortisone —	Slightly improved	—	—	—	129	25 days	Rise in blood urea nitrogen to 191 mg./100 ml. 8 mo. later, despite maintenance therapy
Henneman et al.[16]	8	—	—	—	—	—	Cortisone —	—	—	—	—	—	—	No studies on renal function reported
Phillips[7]	9	1.010	25.0	3	—	11	Cortisone 14	1.020	61.5	25	—	15	27 mo.	Renal function slowly improved over 27 mo.
Present report (Case 2)	10	1.010	38.0	13	—	29	Cortisone 11	1.022	53.0	17	—	21	22 days	Renal function further improved during 74-day follow-up study

In all cases the hypercalcemia was corrected by therapy with ACTH or cortisone. This does not exclude the possibility that failure in treatment has occurred but has not been reported. Nevertheless, the record to date seems impressive. Meticorten in 1 case failed to influence the high serum calcium (Case 10).

The serum calcium fell to normal promptly in all cases.

normal levels of serum calcium obtained from one initial course of steroid therapy continued without further need of retreatment. Two of the patients were kept on maintenance cortisone and continued to have normal calcium levels for the follow-up period.

All patients had evidence of renal insufficiency. In 3 cases this was advanced, with marked azotemia. In general the amount of improvement in

renal function with successful treatment of the hypercalcemic state was inversely proportional to the degree of renal impairment present. As might be expected those with renal failure that was severest and of longest duration had little or no improvement after treatment (Cases 3, 5 and 7, Table 4). One patient died (Case 3) in uremia a week after therapy was successful in correcting the hypercalcemic state, and autopsy showed nephrocalcinosis. Those with less advanced kidney impairment fared better. The results in Cases 9 and 10 were striking, with a return to normal renal function. In addition Cases 1, 4 and 6 (Table 4) showed measurable improvement. No data regarding renal function were given for Case 8.

Other forms of treatment of hypercalcemia in sarcoid have been described. Administration of a low-calcium diet tends to lower the serum calcium levels, although normal values are not necessarily obtained.[5] In addition, chelating agents have been reported to decrease the high serum calcium to normal in sarcoid, but return to high levels occurred when this medication was discontinued.[21]

Summary and Conclusions

The problem of hypercalcemia in sarcoid is reviewed. The frequency, mechanism, clinical symptoms, biochemical findings and differential diagnoses are discussed.

Attention is called to the apparent uniform success in correction of hypercalcemia in sarcoid with cortisone or ACTH. The serum calcium fell promptly to normal levels in all cases during treatment. Maintenance steroid therapy does not appear routinely indicated since relapse to abnormally high calcium levels does not necessarily occur.

Renal function was impaired in all cases of sarcoid with hypercalcemia in which that point was investigated. After correction of the hypercalcemic state with steroid therapy improvement in renal function was significant in some cases. In patients with advanced azotemia little benefit was obtained.

Investigation of the status of calcium metabolism should be routine in all patients with sarcoidosis. If hypercalcemia is found treatment with cortisone or ACTH should be instituted. It is only by early use of these measures that renal insufficiency secondary to nephrocalcinosis can be prevented.

Since this paper was completed, 1 other case of hypercalcemia and renal insufficiency in sarcoidosis successfully treated with cortisone has been reported.[22]

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MEDICAL PROGRESS

SOME ABUSES OF DRUGS IN THERAPY

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THE tremendous advances made in drug therapy in the past decade have created considerable confusion in the minds of many. Most of the new medicinal agents have undoubtedly contributed much to the physician's ability to treat his patients better. Unfortunately, the appearance of new substances has been so rapid as to keep anyone from being able to understand them fully and to evaluate them wisely, much less to employ them with skill in the treatment of the patient.

Around the turn of the century, Osler and other medical leaders were seriously concerned about the profusion of what seemed to them to be either highly questionable or useless preparations. Many of these multiple-ingredient prescriptions had been handed down from generation to generation of physicians without any attempt really to determine their merit.

As a result, hundreds of useless concoctions were discarded, and a healthy skeptical attitude developed concerning drug therapy. Fortunately, this prepared the way for really worth-while advances. The Council on Pharmacy and Chemistry was established, and a much more intelligent and conservative approach was developed concerning all drug therapy. At times it seemed to those who were in the midst of these developments that a period of therapeutic nihilism had descended on the profession. This, of course, was not so, but a natural result of the development of a more conservative attitude toward drugs.

As a result of these developments and in the light of present-day concepts, it is apparent that around 1900 only about one new really worth-while medical substance had been developed in twenty-five years. This is in sharp contrast to what has been happening in recent times. In 1940 about 95 new pharmaceutical specialties were introduced. By 1954 this had risen to 550, and there is no indication that there is any slowing down in the pace. Approximately 90 per cent of all prescriptions call for drugs developed in the last fifteen years. Among this profusion there are some really worth-while drugs, but unfortunately these are not always afforded the recognition they deserve because of the confusion created by the many. Frequently, highly useful agents are developed for special purposes and when used wisely give excellent results. It is essential that the physician learn how to use these new, and some not so new, substances if he is to give his patients the benefits of modern therapy. He must also recognize their limitations and undesirable effects. Finally, it is necessary for him to maintain a critical attitude concerning all preparations until they have demonstrated their merit by satisfying the rigid demands of critical investigators, careful observers and, perhaps as important as the former, the test of numbers and time. The latter factors in the end are most likely to establish the real merits of any medicinal substance since they bring out latent toxicities, and neutralize much of the placebo effect.

The problem has been complicated by the great pressure under which the pharmaceutical industry is forced to operate in a highly competitive field. This has created a situation where a pharmaceutical firm rushes its products out to the market in as brief a time as possible. These firms, together with the Federal Food and Drug Agency, do all they can to ensure that a preparation has merit. The measures on which they depend consist of acute and chronic toxicity studies in animals and limited use in patients. Usually, these tests are satisfactory, but often the factors of wide exposure to many people and the use of the drug over longer periods bring to light undesirable effects and toxicity that greatly limit the value and use of many substances. When these defects appear after a drug has been in use, it is very confusing to the physician who has little time and frequently no inclination to observe, study and report them.

Unfortunately, these factors combined with confusing terminology and complicated dosage patterns have made it nearly impossible for the average physician to understand completely and to employ wisely some of the more useful preparations. Consequently, certain abuses have developed that not only are undermining confidence in drug therapy but also can be harmful to the patient. As a result, conditions such as drug addiction, blood dyscrasias, endocrine imbalances, drug allergies and electrolyte abnormalities are appearing with increasing frequency.

TERMINOLOGY

Undoubtedly, some of the confusion is created by the multiplicity of names. For one agent there may be as many as six or seven trade names to represent individual brands. One of the valuable services performed by the Council on Pharmacy and Chemistry is the assignment of an approved name for each sub-

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stance. This helps considerably, for it leads to more sensible terminology and makes it much easier for the physician to ascertain quickly whether the new agent he has encountered is really something new or a new brand name for something of which he already has knowledge. It is asking too much to expect the average physician to have sufficient knowledge of organic chemistry to form an accurate opinion concerning a substance that has a pharmaceutical manufacturer's trade name and the organic chemical terminology as a guide. It will be most unfortunate for the physician, pharmacist and in the end the manufacturer of pharmaceuticals if the program for assigning official terminology is abolished.

Dosage

The problem of proper drug dosage has always been present, but today it takes on added meaning since some of the recently developed agents have such wide dose ranges. Too often there is a tendency for uniformity in dose that actually amounts to an attempt to fit the patient to the drug rather than to fit the drug to the patient. Unless there is an intelligent adjustment of drug dosage, many failures in therapy will occur even though the drug may be a highly useful substance. This is well illustrated in the use of digitoxin in recent years. In spite of the original teachings of Withering and of many who followed him that the drug should be given until the desired therapeutic or minor toxic effects have been attained, there are still many physicians who think that 1.2 mg. followed by a maintenance dose of 0.2 mg. daily is the proper way to administer digitoxin. This leads to a situation where the initial digitalizing dose is inadequate for many patients while the maintenance dose is frequently too large. Two unfortunate happenings may occur as a result of this dosage pattern. In the first place many patients in need of full, prompt digitalization do not receive it and consequently do not do as well or are slow in recovering from failure; secondly, the maintenance dose when continued long enough, leads to toxic effects, which frequently appear some time later when the patient is not under as careful observation by his physician. To confuse things further, the slowly developed toxicity from too large a maintenance dose is at times very insidious since it does not exhibit many of the commonly observed toxic signs. Patients appear in hospitals with tachycardia and congestive heart failure who on close study turn out to be suffering from digitalis toxicity. The initial beneficial effect of the drug is so gradually replaced by this toxic effect that the change is not detected by the patient or his physician.[1]

The principle of fitting the drug dose to the needs of the patient holds true for practically every medicinal agent. It is therefore difficult to conceive how many of the multiple-ingredient preparations already available and appearing in a continual flood can ever hope to exert maximum therapeutic efficacy except in a limited number of patients. This is made even more difficult when preparations contain agents of widely different pharmacologic action. Therefore, a physician should use great caution in the prescription of multiple-ingredient preparations if he desires to obtain the maximum benefits from his drug therapy.

Errors and careless practice in the use of drugs are not new, but in this era of great therapeutic endeavor they are becoming more important. They not only lead to a poor result when an excellent one should have been obtained but also, owing to the real potency of many of the newer preparations, can and do result in great harm to, or even death of, the patient. Since there are abuses peculiar to the various classes of agents it is expedient to consider a few of them in each of the various drug groups.

Antibacterial Agents

Of all fields of therapeutic endeavor the most rapid and startling advances have been made in the development of drugs to combat infection.

Although the sulfonamides have been in use since 1935 unwise application and poor planning are still observed. Sulfisoxazol (Gantrisin) and sulfadimetine (Elkosin) although much less likely to produce renal lesions can do so if used unwisely. Recently, we observed a patient who had been given sulfisoxazol simultaneously with large doses of ammonium chloride. The latter drug produced a strongly acid urine, and the result was bilateral deposits of sulfonamide crystals in both renal tracts. Unfortunately, the comparative freedom from renal complications has led many to consider these newer sulfonamides to be completely free from toxic properties. This is not true since these substances exhibit allergic or toxic reactions in approximately 2 per cent of patients, the commonest being dermatitis and fever.[2] It is to be noted that some of the lessened incidence of reactions to sulfonamide therapy has occurred because of the less widespread use of these drugs, with the consequent development of a large patient population that has had no previous exposure. If one becomes careless and unwisely uses combinations of the sulfonamides with other widely used drugs there is every reason to suppose that the number of patients with sulfonamide reactions will increase.

Penicillin remains the greatest drug discovery of the present time. It is now a common household item, with millions of medicine cabinets throughout the country hoarding a stock of it for emergencies. This nation is now consuming over 350 tons of it annually.[3,4] Unfortunately, one must face the fact that a large amount of this usage is unwise or totally without value. In spite of ample evidence that it is

of no value penicillin is still being prescribed too frequently in the treatment of viral conditions such as acute upper respiratory infection, influenza and viral pneumonias. Some of this use results when the physician unwisely accedes to the demands of his patients, but more frequently it results from an ill founded belief that it can do little harm and may be helpful in preventing complicating infections. That this opinion is fallacious a look at the facts readily shows. Penicillin is now the most common cause of anaphylactic reactions. Over 200 severe reactions have been reported after its parenteral administration.[3,5] These probably represent only a small percentage of the true incidence. Already over 50 deaths, one from an oral penicillin preparation, have occurred, and the number is steadily increasing.[5] There are many other complications, such as urticaria, which occurs in as high as 6 per cent, serum-sickness-like reactions with fever, arthralgia and malaise in 1 per cent, and various rare types of reactions such as blood dyscrasias, periarteritis nodosa and disseminated lupus erythematosus.[6]

The futility of penicillin prophylaxis in viral and other nonpenicillin-susceptible infections has been ably pointed out by Weinstein.[7] The widespread practice of giving penicillin routinely before and after operation is likewise not as good therapy as it was considered to be at one time. There is a definite risk when this is done. Penicillin-resistant staphylococci develop and may actually increase the incidence of wound sepsis.[8] Hoerr[9] has shown that as many pulmonary complications develop with penicillin as without. Such therapy can lead to the development of superinfections, as well as delays in accurate diagnosis of complications, and, at times, subtly encourages a deterioration in the standards of surgical skill, diagnostic acumen and careful management of the patient.[10] There are, of course, situations where penicillin prophylaxis is warranted — for example, in streptococcal pharyngitis, in the prevention of rheumatic fever and as a measure in the treatment of contaminated wounds, where it can be a useful supplement to thorough débridement.

Streptomycin and dihydrostreptomycin appear to be used more wisely at present and as a consequence fewer cases of vestibular disturbances and deafness are seen. Unfortunately, however, rare cases still appear with severe damage to these functions when these drugs have been given in moderate dosage to patients with severe renal impairment. It must be remembered that they are excreted by the kidney, and when there is sufficient impairment to lead to nitrogen retention, there is real danger in the administration of daily doses of the streptomycin drugs since high blood levels develop rapidly, with resultant damage to the eighth nerve.[11]

Chloramphenicol (Chloromycetin) is now, for the most part, being used more cautiously. Early widespread enthusiasm for this valuable agent was followed by almost complete abandonment and then by its carefully selected use at the present time. Undoubtedly, much of its early use, when it, like penicillin, was being given for a wide variety of situations where it could exert little or no useful effect, was unjustified. After the unfortunate development of bone-marrow depression and death in at least 23 cases up to 1953 it was nearly abandoned.[12] Now, however, a much more sensible attitude has been taken, and its real place in therapy is ensured. In salmonella infections it is a most valuable drug but it is also an effective drug in treating urinary-tract infections, particularly those caused by the proteus organisms, and it is being used increasingly in the treatment of resistant staphylococci. However, chloramphenicol is a drug that is capable of causing serious blood dyscrasia, and therefore patients receiving it must be observed carefully. Adequate blood studies should be done, and long-continued administration without such studies should never be permitted.

The three members of the tetracycline group, chlortetracycline, oxytetracycline and tetracycline, are closely related chemically, and there is very little difference in their behavior when they are administered. Like penicillin, they are being used too frequently in futile prophylaxis. Also too frequently they are given to patients with minor upper respiratory infections. Therefore, severe gastrointestinal disturbances as a result of their use are becoming more common. Diarrhea and anal and vaginal lesions are most troublesome and, at times, can be very disabling. Monilial infections appear and cause mucous-membrane irritation, which can seriously impair the patient's ability to ingest foods. More dangerous than these is the sudden development of staphylococcal enteritis that is fatal in a high percentage of cases.[10]

As in other fields of drug therapy, a large number of preparations combining various antibacterial agents with one or more substances have appeared. One may well doubt the wisdom of combinations of penicillin and sulfonamides, tetracyclines and vitamins, antihistamines and penicillin, and other multiple-ingredient preparations. Such concoctions for the most part add little to therapy and in many cases violate sensible concepts of drug therapy and at the same time increase the cost of the preparation.[13]

Analgesic Agents

Although morphine is an old drug it has certain pharmacologic actions that, if not properly appreciated, lead to poor usage. Frequently, it is given in too large a dose for the need at hand. Apparently, most physicians think of 15 mg. as the standard amount to administer. This dose is frequently more than is necessary. In many cases 8 or 10 mg. will suffice, and there is much less likelihood that nausea, vomiting and other undesirable effects will develop.[14]

In the presence of adrenocortical insufficiency, hypothyroidism and severe liver impairment the dose of all narcotic drugs must be cut by at least half, and whenever possible they should be avoided.

Although it is well known that morphine has an excellent effect in pulmonary edema caused by congestive heart failure, it is also true that it can be detrimental if the cardiac situation is so deteriorated that no improvement is gained by the temporary assistance of the drug. It is well recognized that patients with cor pulmonale, severe pulmonary emphysema and, of course, bronchial asthma are endangered by its administration.

Since all narcotic analgesics have a tendency to increase skin irritability, they should be used with caution, if at all, in patients with severe pruritus.[11] Morphine abolishes much of the reflex activity from receptors in the aortic arch, carotid sinus and pulmonary vessels.[15] This permits wide fluctuations in blood pressure, orthostatic hypotension developing when the patient is placed in an erect position. Therefore, patients who have received morphine for a myocardial infarction or other painful conditions in which a sudden fall in blood pressure might be harmful should be handled with care and kept in a reclining position until the effects of the drug have worn off. Its use in the presence of other hypotension-producing agents such as the ganglionic blockers is fraught with even greater risks.

In the haste to accept the new, desirable features of the old are sometimes forgotten. One of these is the euphoria and sense of well-being that morphine engenders. This feature is highly desirable in patients who are exceedingly apprehensive such as frequently occurs with myocardial infarctions, in which relief of pain is only one factor in wise management during acute episodes. Too often meperidine (Demerol) is given and may successfully relieve the pain only to leave the patient wide awake, apprehensive and, at times, suffering more from his mental status than he was from his physical pain.

Meperidine has proved to be a most valuable drug and now has an established place in therapeutics. Unfortunately, abuses in its use have appeared. It is still administered by many under the impression that it has a specific effect in bronchial asthma. Frequently, it is given to highly agitated and excited patients for anginal pain and, as previously mentioned, to apprehensive patients with myocardial infarction. All these uses of the drug are of highly questionable merit. More serious is the steadily increasing rate of addiction.[16] Unfortunately, about 30 per cent of those addicted are physicians. This should correct any erroneous impression that meperidine has little or no addicting propensity. Patients addicted to it frequently take large doses, up to 4 or 5 gm. daily, and subsequently deteriorate very rapidly.[17]

Nalorphine (Nalline) hydrochloride is a specific antagonist to the narcotic drugs. It reverses their respiratory-depressant effect and consequently is most useful in the treatment of patients who have been poisoned by them. In the addict, however, it rapidly precipitates the withdrawal syndrome. It can be a useful tool for determining the presence of addiction in a suspect since in fifteen to twenty minutes after its administration, acute withdrawal symptoms develop in such patients. Care must be exercised, however, since in patients with well established addiction, the withdrawal effects can be very severe and endanger the life of the patient. Therefore, a small dose of nalorphine, about 2 or 3 mg., should be given as a test dose to a person suspected of addiction rather than the 10 to 20 mg. more commonly administered. It should be remembered that a mild degree of addiction as measured by the nalorphine test develops in a surprisingly short time. As little as 15 mg. of morphine four times a day for forty-eight hours can produce mild withdrawal phenomena.[17] Therefore, care is essential when nalorphine is used in patients who have been taking narcotics for any length of time since the sudden condensing of what would otherwise be a period of three or four days into an hour or two places severe strain on various systems.

Phenylbutazone (Butazolidin) is the most recent derivative of the pyrazalone series of compounds and is used widely for the treatment of pain and inflammation from arthritis and gout. It undoubtedly affords considerable relief in these conditions, as did aminopyrine (Pyramidon), which preceded it. Aminopyrine, however, proved dangerous, and its use in therapy has been almost completely discontinued. Already 23 deaths have been reported subsequent to phenylbutazone therapy.[18] Some of these reflect poor judgment on the part of both physician and patient. In spite of the manufacturer's warning about using the drug with care and following patients closely altogether too many physicians prescribe this drug and make no effort to observe the patient adequately. Since the drug is prescribed for symptomatic relief only, it should be given with the greatest caution.

Salicylate therapy has taken on new meaning in light of recent concepts concerning its action. Unfortunately, too many cases in which gastrointestinal irritation and hemorrhage follow the use of these drugs are still seen.[19] This has taken on added significance since the appearance on the market of preparations containing a mixture of salicylates and cortisone or hydrocortisone. Because the cortisones themselves are not an uncommon medicinal cause of gastrointestinal ulceration, hemorrhage and perforation, their combination with salicylates is certain to result in preparations that must be prescribed with great caution. It remains to be seen just how much of a hazard such compounds will prove to be in practice. Certainly, their use should be avoided in any

patient who has a previous history of gastrointestinal bleeding.

Sedatives and Hypnotic Drugs

These drugs, which have long been a source of considerable difficulty, are rapidily becoming a major national problem. The newer tranquilizing drugs are now also adding to the problem. The suicide death rate from the barbiturates has increased 400 per cent since 1935, and they are now second only to carbon monoxide as a means to suicide.[20] The annual consumption of them now is over 350 tons. Addiction to the barbiturates seems to be increasing in spite of better control by many states. There are no accurate figures available, but authorities at federal narcotic institutions are finding an increasing number of barbiturate addicts among persons admitted.[20] Patients rarely become addicted when the barbiturates are used properly. To produce any degree of addiction in susceptible persons usually takes a dose of 0.3 to 0.4 gm. a day for six weeks of compounds whose hypnotic dose is in the order of 0.1 gm. The withdrawal effect of stopping the barbiturates in an addict is frequently very severe and can lead to convulsions and even death.[20] Since persons who take barbiturates for suicidal purposes or accidentally take an overdose of them are frequently addicts, the withdrawal effects not uncommonly complicate the recovery of these patients, and unless the physician is aware of and alert to this possibility, serious harm may ensue.

In recent months several new sedatives have been introduced into therapy. The trade-name terminology of three of these has provided confusion. They are as follows: Dormin, the antihistamine, methapyrilene, a moderately effective sedative sold over the counter to all who wish to obtain a sedative without a physician's prescription; Dormison, an acetylene-derivative methylparafynol and a rather weak sedative; and Doriden, the brand name for glutethimide, an effective, moderately long-acting sedative. These, as well as Noludar, a brand of methyprylon, and Valmid, a brand of ethinamate, are all nonbarbiturate-type sedatives. It is too early to draw definite conclusions concerning these preparations, but enough evidence has accumulated for one to deplore the widespread, uncontrolled use of antihistamines as sedatives. If they are effective at all, they must inherently carry with them the same dangers as other sedative drugs. Already, a death has followed the use of methapyrilene, and patients have appeared who have been taking large amounts with harmful effects.[21] Although none of these newer sedatives are barbiturates and are metabolized differently by the body, they must not be considered harmless. No cases of addiction to them have appeared as yet, but it is probably only a matter of time before some do. Any drug that excites, distorts or sedates mental function has inherent in it the possibility of causing addiction.

Perhaps one of the most interesting advances during the past three years has been the development of a new class of agents that, although having some of the characteristics of the sedatives, do not have the same end effect or behave like the true sedatives. These substances are promethazine (Phenergan), chlorpromazine (Thorazine), *Rauwolfia serpentina,* its semipurified derivative, Rauwiloid, or the crystalline derivatives, reserpine and raunorine, meprobamate (Miltown, Equanil), azacycolonol (Frenquel) and the more recent benzilic acid derivative, benactyzine (Suavitil). They are being used in fantastic quantities to bring about a reduction in tension or excitement and to produce a calm or tranquil state. Some of these substances supply a therapeutic need not only in mild emotional aberrations but also in patients with serious mental disease. Most of them, when used wisely, are of value and for the most part without serious toxic effects. The phenothiazines, especially chlorpromazine, do produce an obstructive type of jaundice, which, although usually mild, can be serious. Usually, prompt cessation of the drug leads to clearing of the jaundice in approximately ten days to two weeks. Some patients, however, have had jaundice persist for months, and at least 3 fatal cases of liver failure have been attributed to them.[22-24] Agranulocytosis has been reported in a few cases from the use of chlorpromazine.[25,26] Although serious reactions are rare in the millions who have received chlorpromazine, they are a warning that patients should be selected with care and followed carefully when the drug is used in full dosage for any length of time. Unless there is an immediately beneficial effect of real importance, the drug should be discontinued. Furthermore, at the first appearance of even minor indications of a toxic effect, such as loss of appetite, adverse change in mental status in one formerly doing well, skin rashes, fever, gastrointestinal disturbances, anemia or depressions in the white-cell count, the drug should be stopped. Since chlorpromazine is detoxified for the most part by the liver, it should be given with great caution to patients with liver impairment.

R. serpentina and its crystalline derivatives, reserpine and raunorine, like the phenothiazine compounds, are being used successfully for emotional-tension states as well as in hypertension. There is considerable confusion over dosage schedules for this preparation also. In general, 0.1 to 0.25 mg. of reserpine once daily is satisfactory for mild hypertension. This small dose is less likely to produce undesirable reactions, consisting of nasal congestion, occasional epistaxis, gastric irritation, with activation of an old or formation of a new peptic ulcer, and mild to severe irritation of the colon. The last complication may lead to diarrhea together with confusing symptoms and signs that have been mistaken for an acute condition of the abdomen and have led to an appen-

dectomy or cholecystectomy in rare cases. More serious, and certainly more subtle, is the development of mental depression, which occurs much more often than is realized and may lead to serious anxiety and even suicide.

Higher doses of *R. serpentina* increase the severity and frequency of these reactions and can, in daily doses of 5 mg. or more, produce a state of parkinsonism.

The exact status of other drugs of this type is as yet not clear. Undoubtedly, much of the response to any of these drugs carries a large placebo element. Therefore, it is wise for the physician to discontinue any of them from time to time and to re-evaluate their status.

Cardiovascular Drugs

Certain confusions that have crept into treatment of various aspects of cardiac disease are leading to the abuse of what would otherwise be excellent agents. The misuse of digitoxin was mentioned above under dosage problems.

Nitroglycerin, after many years of proper sublingual use, is now being offered to physicians in the form of a slow-release preparation to be given by mouth. Nitroglycerin is much less active orally: 2 mg. four times daily has been given for periods of one month without any observable effect.[27] It is therefore difficult to conceive how a total dose of 2 mg. in slow-release form could have much more than a placebo effect in angina pectoris.

A word of caution is in order about the use of sublingual administration of nitroglycerin. Patients who are started on the drug should be cautioned about syncopal attacks, and initial doses should be taken with the patient in a recumbent or sitting position. Severe injuries have resulted from such syncopal attacks unless patients are warned.

There are still too many cases of poisoning from ammonium chloride. Large doses of 4 gm. or more should never be given if there is impairment of the liver or kidney to any degree. When ingested, the ammonium moiety is converted into harmless urea by the liver, but in the presence of liver disease, toxic amounts of ammonia may accumulate and seriously harm the patient. The chloride is excreted by the kidney, which for the first two or three days uses sodium to handle the excess acid, and accordingly an excellent diuresis occurs for three or four days. Almost immediately on being faced with excess acid the kidney begins synthesizing ammonia to conserve base. In three or four days the kidney is synthesizing large amounts of ammonia, which is converted to ammonium by the action of the tubule cells. The ammonium then combines with the chloride, and, as a result, as much ammonium chloride is being excreted as is being ingested. Consequently, nearly all diuretic effect is lost, and the drug has little effect by the end of the fifth day, thus making it fruitless to administer it for a longer period.[28] If, however, there is renal impairment and decreased ability to synthesize ammonia, there is a real danger of acidosis and coma. If the drug is continued for long periods considerable nitrogen is lost. Since this is derived from amino acids, its loss can cause a deficiency in protein synthesis and subsequent hypoproteinemia.

In spite of the many claims made first for one and then another of the digitalis preparations, nearly all problems can be met by the wise use of digitalis leaf and Digoxin. When the patient has been adequately digitalized and is being maintained on digitalis under conditions where frequent or close observations are not possible, the use of the powdered leaf has much merit since nausea and vomiting are easily recognized signs of toxicity that occur more commonly with this preparation.[29] If the leaf is used, it is wise to select one brand and keep the patient on it. This avoids differences in potency that exist between brands and ensures a more even digitalization. Furthermore, when a patient who has been doing well begins to do less well it may be due to a partial loss of digitalization that occurs more commonly than suspected. Usually, three or four days during which the dose is doubled will correct the difficulty. In some patients this redigitalization is necessary every two or three months.

In patients who have serious myocardial damage and in any situation where the toxic effects of a cardiac glycoside might prove dangerous, the use of Digoxin is most satisfactory. Digoxin has the merit of acting promptly, within ten to twenty minutes, when given intravenously, with its maximum effect exerted by two hours, and if a toxic effect is produced it is lost in twenty-four to forty-eight hours. These are the factors that have made it a favorite in the management of the seriously ill cardiac patient until the situation is stabilized. Many physicians then prefer to shift to the leaf for the long-term management. However, if a purified glycoside is desired, Digoxin is the one of choice since it has been shown that of the various purified glycosides it more frequently gives the easily recognized signs of toxicity — nausea and vomiting.[30]

Gastrointestinal Drugs

Drugs administered in the management of most disturbances of gastrointestinal function consist of the antacids, antispasmodics, cathartics and the antibiotics. The selection of antacid therapy has shifted in the last decade to the almost exclusive use of various aluminum hydroxide, magnesium trisilicate or carbonate mixtures. Although there is certainly much merit in these mixtures, unfortunately, some of the valuable features of the old Sippy powders, contain-

ing equal amounts of sodium bicarbonate and calcium carbonate, have been forgotten. Although almost everyone agrees that the newer mixtures are effective in nearly all situations and are certainly less likely to produce renal stones and systemic alkalosis, they do not as effectively or as quickly lower stomach pH as the Sippy powders. In the presence of a gastric ulcer or a very painful duodenal or marginal ulcer, the use of Sippy powders to promote quick, highly effective neutralization of stomach acid not only will give the patient far more effective relief of the pain but also will promote more rapid healing and shorten the hospital stay and period of disability. In the presence of good renal function, adequate fluid intake and use limited to acute phase, there is very little possibility of toxic effects from the Sippy powders. Once the patient is over the acute phase, a shift to the aluminum hydroxide mixtures should be effected, and thus the maximum benefits may be obtained from both types of antacids.

The bewildering number of gastrointestinal antispasmodic drugs has created a great deal of confusion. Each is useful in bringing about relaxation of gastrointestinal spasm. The newer preparations vary from those like methantheline (Banthine) and propantheline (Probanthine), which, when administered in effective dose, give the same side effects as effective doses of the belladonna alkaloids, to those with a mildly relaxing action and practically no distressing effects. In spite of the plethora of these agents, the vast majority of patients requiring a gastrointestinal antispasmodic will receive excellent effects when tincture of belladonna is administered in the correct way and in adequate dose. If ever there was a preparation that required fitting the dose to the patient's needs, it is tincture of belladonna. Since adequate therapy may vary from 8 to 30 drops four times a day at approximately six-hour intervals, it is a preparation well suited for adjustment in dose, and with it one can titrate the patient's needs very successfully. Many of the newer agents, of course, do not have as many untoward effects as belladonna, such as mouth dryness, occasional blurring of vision or, rarely, retention of urine, and this lack of side effects is usually considered desirable. This would be true if the newer agents did as satisfactory a job as the belladonna alkaloids in breaking down severe spasm. Unfortunately, they do not give relief in severe situations and do not readily lend themselves to multiple adjustments in dose. With tincture of belladonna, on the other hand, the very side effects can be used as guides to adequate dosage. If the pain and spasm are still present and the mouth is not dry, the dose must be increased until there is a good degree of mouth dryness. If blurring of vision becomes annoying, the dose level for that patient must be lowered or belladonna discontinued. It is also important to remember that retention of urine may occur in the exceptional patient when large doses of belladonna alkaloids are given. This usually occurs in males who have prostatic hypertrophy and in any patient who has a weakened detrusor reflex, or weakened bladder muscles. There is one other untoward effect from the belladonna alkaloids that, although rare, can create much confusion if not recognized by the physician. In a very rare case, usually in an older arteriosclerotic patient, periods of mental confusion with hallucinations occur. These are also created by methantheline. Usually, the hallucinations take the form of elaborate patterns with considerable detail to the object seen by the patient. These symptoms clear promptly when the drug is withdrawn.

Cathartic Agents

The unwise use of these agents has become a serious problem. Mineral oil, once thought to be harmless, is now known to be a very real source of serious lung damage. The more closely one looks for cases with fibrosis, repeated pneumonias and severe lung damage from the chronic intake of mineral oil, the more cases one finds.[31] The lesions are not always in the lung bases, as is commonly thought, but may be in one lung or one lobe of one lung. Much depends on the posture the patient assumes after taking the nightly dose of mineral oil. If he lies on the right side, for example, the right middle lobe may show the chief damage. Certainly, the chronic use of mineral oil should be condemned.

A bit of common sense regarding diet, proper intake of water, establishment of good habits and an occasional use of such mild agents as milk of magnesia, aromatic elixir cascara sagrada and the rare enema will successfully relieve nearly all cases of simple constipation.

Hormone Therapy

The great advances made in this field have unfortunately created one of the largest groups of patients with iatrogenic disease. One sees patients with hypothyroidism created by long-continued use of thyroid hormone, Cushing's syndrome created in many cases by improper use of cortisone, in female patients taking estrogens for twenty to thirty years and in males taking androgens for years and all kinds of adrenocortical extracts taken for a wide variety of complaints. This is indeed an unfortunate situation. Not only are many of these substances expensive but also they are capable, at times, of producing irreversible harm. A thyroid gland suppressed for many years by an extraneous source of thyroid becomes incapable of responding properly when the hormone is withdrawn, and thus a thyroid cripple is created. Too often there is very little reason for the hormone to have been given in the first place. Unless there is definite evidence of thyroid hypofunction, as measured by ade-

quate laboratory procedures and adequate symptomatology, thyroid medication should not be given. Once a patient is on thyroid therapy, his status should be reviewed at intervals to determine if the need still exists. Fortunately, the combinations of thyroid with other drugs commonly seen in the past have nearly disappeared.

Cortisone, hydrocortisone and the newer synthetic steroid hormones of this type have such widespread use in therapy that it is difficult as yet to separate good from questionable use or abuse in many situations. Certainly, it is highly questionable whether they should ever be used systemically for atopic eczema, in the presence of a history of gastric or duodenal ulcer, congestive heart failure, diabetes mellitus and infectious states such as tuberculosis. Recently, combinations of these preparations with salicylates have been made and are finding widespread use. Certainly, the physician prescribing such combinations must take measures to protect the gastrointestinal tract from ulceration and hemorrhage.

Perhaps of all the hormones, the estrogens are most widely used and abused. We have recently seen a female patient who was still taking estrogen therapy twenty-two years after having both ovaries removed at the age of eighteen years. She still complained of vasomotor phenomena and was certain the only relief she had ever received was while she was taking estrogens. Attempts to withdraw the estrogens had ended in failure since severe vasomotor phenomena always developed and various physicians let her return to the drug. This experience is not unique, and nearly every physician sees patients who have taken estrogens for long periods. Interestingly enough, in castrated male patients put on large doses of estrogens for long periods, withdrawal of the hormone can precipitate similar vasomotor phenomena, so it appears that the hormone in some manner creates abnormal vasomotor responses as a withdrawal effect. In other words, these are actually cases of physical dependence created in certain patients by the use of the hormones. It should therefore be apparent that this form of drug addiction should receive the same treatment as that of other drugs — namely, withdrawal, followed by adequate psychotherapy and avoidance of future exposure to the drug.

Vitamins

Vitamin preparations and vitamin combinations with other drugs are still used very extensively. In spite of ample evidence to the contrary they are being prescribed by physicians, advertised by radio and television programs and taken by the public for the prevention of upper respiratory infections, for the creation of more energy, to help control infections, to treat skin conditions and to help treat arthritis. Vitamin B_{12}, the most recent preparation to be used widely, is, for the most part, replacing liver injections as a form of placebo therapy for a multitude of complaints. The tragedy of all this abuse of good nutritional agents in therapy lies in the cost that burdens the unsuspecting patient even though the placebo effect has resulted in relief from his symptoms.

In recent years, some ridiculous concoctions that are reminiscent of the famed theriac of Claude Bernard, a potion made by tossing in leftovers from many prescriptions, have appeared. Some of these formulas contain twenty items. Apparently, attempts are made to add a little bit of everything known to have any role in human nutrition. It is a surprising commentary on present-day therapeutic intelligence not only that such preparations should appear but also, and worse still, that they find acceptance. It is fortunate that such conglomerations are usually harmless. Hematologists have complained that the folic acid in some of these preparations masks pernicious anemia. A search of dozens of multiple-vitamin preparations revealed only two that did not contain folic acid as one of the components. The tragedy of this type of therapy is its uselessness and its cost to the unfortunate patient.

Finally, a word should be included about the use of vitamins in combination with other drugs. Most of these are valueless. Perhaps the most recent combination has been that of vitamins with antibiotic preparations in the hope that the addition of an adequate supply of vitamin to the antibiotic would help the patient meet more adequately the stressful situation created by the infection and aid in its treatment. However, there is no evidence that such combinations add anything to the therapeutic results.[13]

Summary and Conclusions

Some of the problems of modern therapy and the use and abuse of certain classes of drugs in therapy are discussed. Although many new preparations are available they have not replaced many of the older agents. Newer knowledge concerning dose factors, mode of action and undesirable effects of various drugs is reviewed. The importance of fitting a drug to the patient's needs is stressed. Unfortunately, there are still altogether too many undesirable combinations of drugs and useless preparations in use or appearing for use.

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MEDICAL INTELLIGENCE

MULTIPLE MIXED TUMORS OF SALIVARY GLANDS

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M. STUART STRONG, M.D.†

BOSTON

THE purpose of this communication is to present a case of two mixed tumors occurring simultaneously, involving the parotid gland and the homolateral submaxillary gland. The rarity of this occurrence renders this case of interest. No attempt is being made to give support to the concept of multicentric origin of mixed tumors on the basis of this report.

Foote and Frazell[1] have cited 3 cases of multiple mixed tumors of the salivary glands: a patient of Dr. Danely Slaughter who had a parotid mixed tumor and subsequently one of the homolateral submaxillary gland; a case of Dr. Ralph Braund that presented two mixed tumors in the same parotid gland; and a case of Dr. William O. Wuester with three histologically typical mixed tumors, two occurring in the right and the third in the left parotid gland. Pricolo[2] and Brown et al.[3] have each recorded 1 patient with bilateral mixed tumors of the parotid gland. Beale[4] discussed a thirty-five-year-old woman with bilateral parotid tumors of approximately three years' duration; no surgery was performed, and there was no microscopical evidence of mixed tumor. Wilson and Willis[5] have reported a case of right and left submaxillary mixed tumors of six years' duration, occurring in a sixteen-year-old boy. Spring[6] described a sixty-four-year-old woman with a three-year history of a tumor the size of a child's fist in the right premolar region, with eventual involvement of the soft palate. Six years later, there was a malignant recurrence in the region of, but not involving, the submaxillary gland. In reading his description of the case, one questions whether the submaxillary gland was actually involved. There is a further question

FIGURE 1. *Photograph, Demonstrating Enlargement of the Right Parotid and Right Submaxillary Glands.*

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whether this represented a malignant mixed tumor of the palate with recurrence since lesions in this site are more apt to be malignant. Consequently, it is

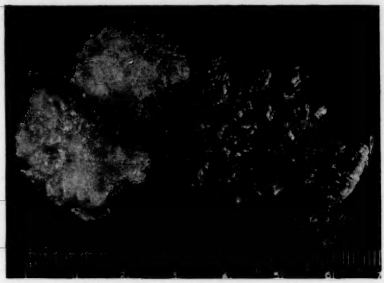

FIGURE 2. *Gross Specimen of the Entire Right Submaxillary Gland, Showing Tumor in Cut Section.*

doubtful whether this case can be considered one of multiple mixed tumors of the salivary glands.

CASE REPORT

M. G. (M.M.H. 382894), a 62-year-old Negress, was first seen on June 29, 1955, for asymptomatic swellings of the right side of the neck that she believed to have been present

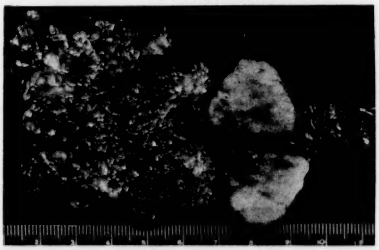

FIGURE 3. *Gross Specimen of Superficial Lobe of the Right Parotid Gland, with Bisected Tumor.*
Note the poor delineation of tumor tissue.

for the past 11 years. At that time she had been seen at a neighboring clinic with complaints referable to the menopausal syndrome, and admitted having the cervical masses for 4 or 5 years. Examination on July 15, 1944, revealed 2 hard and discrete "glands" in the right side of the neck, at the angle of the mandible and at the submaxillary region. It was thought then that she might have Hodgkin's disease, leukemia or lymphocytoma.

The past history was not remarkable. A cervical abscess (site unknown) had been incised and drained in childhood. At 19 years of age she had a tonsillectomy and adenoidotomy, and at 33, a subtotal thyroidectomy for hyperthyroidism. Approximately 12 years before admission a nasal cyst was excised. The family and social histories were noncontributory. Review of the systems was negative except for the neck tumors and arthritis.

Physical examination disclosed bilaterally enlarged tonsils. A firm, nonmobile mass, measuring 3 by 3 cm., was attached to the right parotid gland at its inferior margin, with a firm, mobile submaxillary enlargement, measuring 4 by 6.5 cm., on the same side (Fig. 1). There was no significant lymphadenopathy. Hospitalization was refused.

Subsequently on October 3, 1955, the patient returned complaining of sharp pain in the right ear and pain radiating from the angle of the jaw upward along the preauricular area. She consented to hospitalization because of the intensity of the pain, and was admitted to the hospital on October 24.

Physical examination revealed an obese woman weighing 90.7 kg. (200 pounds). Examination of the ears, nose and throat was negative except for recurrent tonsillar tissue. There were no demonstrable sensory changes of the tongue. The tumors of the neck were as previously described, without any significant enlargement. The thyroid gland was small,

FIGURE 4. *Photomicrograph of the Specimen Seen in Figure 2, Showing Typical Cords of Tumor Cells.*
Two areas of squamous metaplasia can be seen in the lower central field.

and the trachea was in the mid-line. A healed collar incision was seen. The remainder of the physical examination was within normal limits except for a ventral hernia, uterine fibroids, a mitral systolic murmur, varicose veins and arthritic changes of the hands. There was no significant lymphadenopathy, and the cranial nerves were intact.

Examination of the blood showed a hemoglobin of 12.5 gm. per 100 ml., with a hematocrit of 41.5 per cent and a mean corpuscular hemoglobin concentration of 31 per cent. The icteric index was 5 units. The white-cell count was 6900, with 80 per cent neutrophils, 17 per cent lymphocytes and 2 per cent monocytes. The blood urea nitrogen was 11 mg. per 100 ml. Urinalysis was negative. X-ray examination of the chest was within normal limits.

On the day after admission, the right submaxillary gland and the right superficial lobe of the parotid gland were resected (Fig. 2 and 3). Frozen section was negative for cancer.

The pathological diagnosis was mixed tumor of the parotid gland, with focal muscle degeneration and negative lymph nodes, and mixed tumor of the submaxillary gland, with a mucoepidermoid component. Microscopically, the

submaxillary-gland tumor consisted of narrow and broad cords of irregular and columnar cells having a moderate amount of eosinophilic cytoplasm and oval, moderately chromatic nuclei, with occasional nucleoli and without mitotic figures (Fig. 4). In addition, there was moderate acinar formation within the lumen of which there was a homogeneous eosinophilic material occasionally showing basophilic patches (Fig. 5). Some of the cells in the acinar lining contained a basophilic mucoid substance. Several areas of squamous metaplasia were noted with central keratin "pearl" formation. The cells generally were uniform. A few small areas of cell necrosis were present, with plasma-cell infiltrate. The stroma consisted of narrow and broad bands of hyalinized collagen, and areas of basophilic changes of a mucoid nature were seen within these bands.

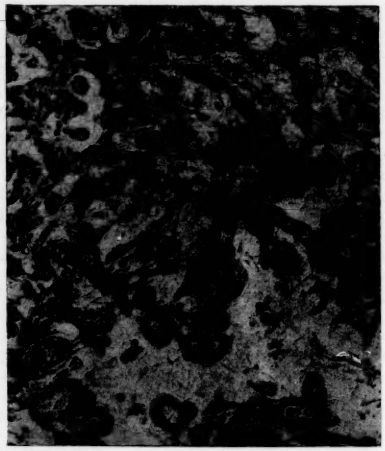

FIGURE 5. *Photomicrograph of the Gross Specimen Seen in Figure 3.*
Note the typical mixed-tumor pattern with loose myxoid stroma and acinar formation.

A few areas of pseudocartilage were noted. All sections showed a moderately thick hyalinized fibrous capsule, which was free from tumor invasion.

The pattern of the parotid-gland tumor was that of the usual mixed tumors, with thin cords and small alveoli and abundant myxoid stroma. There was abundant, dense, hyalinized connective tissue in which very thin compressed acini were found. No areas of squamous metaplasia or microcysts were noted. A very thin incomplete fibrous capsule separated the tumor from the normal salivary tissue.

SUMMARY

The literature on multiple mixed tumors of the salivary glands is briefly reviewed. A case of simultaneously occurring mixed tumors of the right parotid gland and the homolateral submaxillary gland is presented.

We are indebted to Mr. Leo Goodman, of the Mallory Institute of Pathology, Boston City Hospital, for the photographs.

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BY THE LONDON POST

Medical Leadership — Prescription for Health

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LONDON, ENGLAND

THE medical profession has long been recognized as one in which individualism may flourish. On the other hand, since the advent of the National Health Service there has been a constant tendency for an independent medical profession to be transformed into a service offering little place for the individual point of view. It is for this reason that strong medical leadership is essential today. Unfortunately, it is the very fact that individualism is such a strong characteristic of physicians that makes the profession so vulnerable to outside control because it is difficult to obtain a universally acceptable and representative leadership.

Many interests are involved. The Royal Colleges represent the interests of the physicians, the surgeons and the gynecologists, and the universities the academic field, and although the British Medical Association should be able to represent the views of the whole profession, by tradition its main support has come from the general practitioners. The *British Medical Journal,* in a leading article, recently discussed certain aspects of the problem. In particular, it considered the part that the Royal Colleges should play in guiding the medical opinion of the day. The Royal College of Surgeons has been active in promoting research projects and planning postgraduate education. The Royal College of Physicians, the oldest medical college in Britain, has tried to maintain the academic tradition of "persons that be profound, sad and discreet, groundedly learned and deeply studied in physic." The college has also played a leading part in medicopolitical matters since the National Health Service began, and the President, almost by virtue of his office, has found himself in the position of chief negotiator in matters about which differences have arisen between the medical profession and the Government.

Partly because of this peculiar role that has fallen to the President, the office has been filled by only two fellows of the College during the last sixteen years, Lord Moran being president from 1941 to 1950, and Sir Russell Brain just having entered his seventh year of office. Such long terms of service have been criticized by the *British Medical Journal* although it is conceded that the circumstances have been unusual and that there have been grounds for arguing that it is better for the negotiations to be in the hands of men who have gained experience of such matters.

In reply to the leading article, Sir Russell Brain stressed the point that it is the aim of the Royal College to remain free to express independent views and to act or withhold action in any field of medicine, including its relations with the State. Sir Russell would resist any attempt on the part of the British Medical Association to obtain a position of exclusive privilege and power in medicine.

It is clearly of the utmost importance for the profession to remain independent, and it may be that the Fellowship for Freedom in Medicine that was created largely by the late Lord Horder will in time fulfill a more powerful role. Meanwhile, it is important to recognize that a strong, united leadership is essential if this independence is to be maintained.

* * *

The Royal Society of Health recently held its annual congress, at which the different sections discussed a wide variety of subjects.

Addressing the Section of Preventive Medicine, Professor C. F. Brockrington called for a service of community health linked to the family and for a continuous study of disease and ill-health within the community. There had recently been too much emphasis on the hospitals, and a new service for community care would become the friendly rival of the hospital service and would tend to reduce the calls upon the hospitals. Recent studies favored the view that the care of the sick in their houses was better for them than admission to the hospital. He thought that the community service could be developed by a merger of the public-health and general-practitioner services, the latter working in close liaison with the midwife, the medical officer of health and all others employed by the local health authorities. He pleaded for the development of health centers where the general practitioner would have both the scientific and the social instruments available for such a modern approach to health.

The section of the congress that aroused most popular interest was that on occupational health, where one of the main topics for discussion was the health of the traveling business executive. The general conclusion seemed to be that the tired business man has never been more tired than he is today. Not only has he no refuge at home or in the office from the strain of his massive labors but also the journey between is the most exhausting part of his day. A trip to the city in a deeply cushioned chaffeur-driven car is no help in these days of congested roads. It probably gives rise to nervous tension, and the executive's secretary can usually tell when he has had a rough journey to town. Dr. Buckland, of London Transport, claimed that travel by public transport vehicles is less tiring than driving one's own motor car. He suggested that the rush-hour crowds could be thinned if everyone gave the nervous system a few minutes to cool off before attempting to do battle with the rest of the crowd.

Long journeys abroad were also criticized. At best, traveling abroad is stimulating and provides a welcome respite from day-to-day anxieties. But long and busy visits are often not a happy release from the normal day's work, but simply involve harder work than the usual day in the office or factory at home. In particular, whatever Mr. W. Somerset Maugham may say, the tropical journey is exhausting. It does not consist of lazy afternoons and cheerful evenings of drinking — on the contrary, the pilgrim of commerce to a tropical isle must expect to rise early and sit up late, working all the time for six and a half days a week.

The only solution to the problem seemed to be to advise the business executive to relax. He would do better to make journeys abroad by sea rather than by air; he would do better to travel to his office by train or bus rather than by his own motor car. The *Times,* commenting in a leading article, suggested that he would do better still if he remembered that there is nothing so restful as the column on the march with "Boots, boots, boots, boots, movin' up and down again." The business executive should therefore walk afoot whenever he has the chance. Indeed, the position was well summarized by Dr. C. F. White, formerly, medical officer of health for the City of London, who claimed that people of high national importance are wearing themselves out prematurely. If only they would go more slowly they might have much longer in which to make their contribution to the national economy.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42261

PRESENTATION OF CASE

A twenty-eight-year-old woman entered the hospital because of hematuria.

Seven years previously an episode of painless hematuria occurred one week before the termination of a normal pregnancy. Ten months later there was a recurrence of bleeding, which persisted. Three years before entry the right kidney was explored at another hospital. A nephropexy was done because the kidney lay low and in a poor position for ureteral drainage. No other abnormalities were found. No further bleeding was noted until eighteen months later, when painless hematuria recurred and persisted for eight months. There was further bleeding beginning six months before admission. The color of the urine varied from cherry pink to dark red, with occasional clots. A "pressure pain" in the right flank that did not radiate was occasionally noted. There was no history of chills, fever or urinary symptoms. A transfusion of blood was given one week before entry because of "low blood."

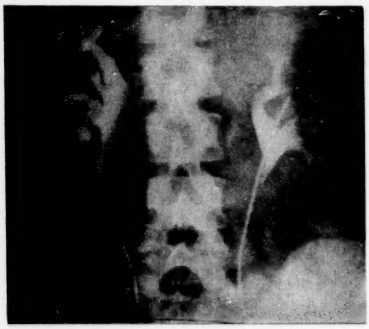

FIGURE 1. *Bilateral Retrograde Pyelogram.*

Physical examination showed a well nourished woman in no distress. Examination of the abdomen revealed an operative scar in the right flank and minimal tenderness on deep palpation over the area of the right kidney.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 60 diastolic.

The urine was grossly bloody and gave a + test for albumin. Examination of the blood revealed a hemoglobin of 11.4 gm. per 100 ml. and a white-cell count of 8200. The platelets were normal. The nonprotein nitrogen was 23 mg. per 100 ml. The prothrombin content was 100 per cent. The bleeding and clotting times were normal. Cystoscopic examination showed blood coming from the ureteral orifice on the right; culture of the urine from the bladder grew out a few colonies of *Haemophilus influenzae*; cytologic examination for malignant cells was unsatisfactory. A retrograde pyelogram was normal (Fig. 1).

An operation was performed on the third hospital day.

DIFFERENTIAL DIAGNOSIS

DR. SYLVESTER B. KELLEY*: First, let us consider the type of patient with whom we are dealing. A twenty-eight-year-old woman ought to be in the prime of life, but here was one with signs of serious trouble. We immediately think of neoplasm of the kidney or bladder, urinary calculi, tuberculosis, polycystic kidney disease or acute inflammatory lesions in the bladder. The absence of concomitant findings helps eliminate some of these possibilities.

The long duration of the symptoms and the youth of the patient make a diagnosis of neoplasm unlikely. Cancer of the kidney is, of course, most common in the fourth and fifth decades. Even though Mintz† once reported a series of patients with known neoplasms of the kidney who got along relatively comfortably for more than five years without benefit of surgery, I should put cancer of the kidney low on the list of possibilities in this case.

It also would be unusual for a cancer of the bladder that was untreated to develop over a period of seven years, without causing more symptoms locally, such as suprapubic pain, urinary frequency, dysuria and tenesmus. In a male we can frequently make a diagnosis of cancer of the bladder on the basis of a history of terminal hematuria. Deprived of that helpful distinction between initial and terminal bleeding here, I think we had better consider cancer of the bladder another unlikely possibility.

*Visiting urologist, Massachusetts General Hospital.

†Mintz, E. R. Natural history of some renal tumors. *New Eng. J. Med.* 213:251-257, 1935.

The usual manifestation of calculi in the urinary tract is pain: pain so severe that the patient cannot lie quietly. Here, we are told of a "pressure pain" in the right flank. The "right flank" is a vague term, but, in this case, let us assume that the pain was localized in the costovertebral angle and that it was associated with the slow accumulation of blood within the kidney pelvis. At any rate it is not the agonizing pain of a ureteral stone.

With polycystic kidneys the patient probably would not have had a "normal pregnancy." She also was quite young to have symptoms from such an anomaly, and so let us discard this possibility.

Shortly after the termination of pregnancy, a latent tuberculous lesion of the kidney may become obvious. But this would be accompanied by other findings, including loss of weight, chills, fever, pyuria and probably urinary frequency and dysuria. This patient was altogether too healthy to warrant any more than a brief consideration of tuberculosis. She also was free of the marked urinary frequency, dysuria, urgency and strangury that characterize an acute infection of the bladder.

Infection of the urinary tract with the influenza bacillus is sometimes accompanied by calcification within the renal tubules. The absence of radiopaque densities in the renal parenchyma, however, would minimize the etiologic significance of this organism in the urine.

In a patient whose hemoglobin is down to 11.4 gm. per 100 ml., a blood dyscrasia must be considered. In the blood studies available, however, we find nothing to substantiate such an explanation.

The cystoscopy done at the time of the bleeding provided important evidence concerning the source of the blood. The examiner might have helped us further by describing the type of flow from the ureteral orifice: when the fluid drips constantly, a lesion of the ureter is suspected; when it comes in spurts of a few drops followed by a pause, one visualizes a normal peristaltic flow down an intact ureter.

The chief benefit from the remark "cytologic examination" is a warning that we must not rely too much on the interpretation of the Papanicolaou smear when considering the possible malignant processes in the upper urinary tract. Normal or traumatized transitional cells from the renal pelvis and ureter are mistaken for cancer cells in a significant number of cases.

May I see the x-ray films?

DR. C. C. WANG: I am not sure that the retrograde pyelogram on the right is entirely normal (Fig. 1). There is some fuzziness of the medial border of the renal pelvis on the right, but no definite tumor mass is seen in this region. The calyxes on both sides are nearly normal in appearance. The renal outline on the right is not well seen. There is no evidence of opaque stones.

DR. KELLEY: I agree with Dr. Wang that the pyelogram is not quite normal. The irregularity of the medial border of the right kidney pelvis is consistent with malakoplakia or even ureteritis cystica. But in either case I should have expected to find similar lesions in the bladder, and so I shall abandon that lead and attribute the irregularity of the renal pelvis to scar from previous surgery.

Concluding that these various diagnostic possibilities are unlikely, I resort reluctantly to idiopathic hematuria, that undesirable designation, as an explanation for this patient's symptoms. In cases of this kind in which I have been forced to perform nephrectomies for the prevention of further blood loss, the pathologist has been unable to demonstrate any abnormality of the kidney.

DR. WYLAND F. LEADBETTER: Dr. Kelley, what do you think the cause of idiopathic hematuria might be?

DR. KELLEY: No one knows. It is a pigeon-hole into which these cases of bleeding from a kidney without deformity of calyxes or pelvis are put. In some cases it may be associated with a tiny varix, which is not found by the pathologist. If it is associated with a necrotizing papillitis that should be obvious.

DR. EARLE M. CHAPMAN: Could I ask if that fuzziness of the lateral surface might be a small hemangioma?

DR. KELLEY: Yes; I did not mention that because I have never seen one. It is a very unusual type of disease.

DR. CHAPMAN: The record did not say whether or not the patient had hemangiomas of the skin, or on the surface of the body.

DR. KELLEY: She may have had something like that.

A PHYSICIAN: Do you think that the calyxes are normal?

DR. KELLEY: I attributed the dilatation of the calyxes to overinjection of dye; they seemed quite clear-cut. I should say that they were normal.

DR. WANG: I think that the calyxes are slightly dilated because of overdistention.

DR. BENJAMIN CASTLEMAN: Dr. Leadbetter, you saw the patient; will you tell us your opinion?

DR. LEADBETTER: This was an interesting diagnostic problem. I saw this patient three years before admission, when she was bleeding from the right kidney, as she was on this admission. At that time pyelograms and ureterograms, which were very carefully performed, seemed to show an absolutely normal pelvis and ureter. The only abnormality was some degree of ptosis. I did not operate on her because of the ptosis; I operated to find the explanation for the bleeding. The right kidney was normal in external appearance. I opened the pelvis and examined it with a pyeloscope, an instrument that allows us to look at the individual calyxes; I saw nothing. A nephropexy was done, after which she was free

from bleeding for eighteen months. At this admission she had exactly the same picture; I did not think that the pyelogram was quite normal so I explored the kidney.

Clinical Diagnosis

Hematuria, right kidney, cause undetermined.

Dr. Sylvester B. Kelley's Diagnosis

Idiopathic hematuria.

Anatomical Diagnosis

Angioma of kidney.

Pathological Discussion

Dr. Leadbetter: When I opened the pelvis and examined the interior of the kidney with a pyeloscope,

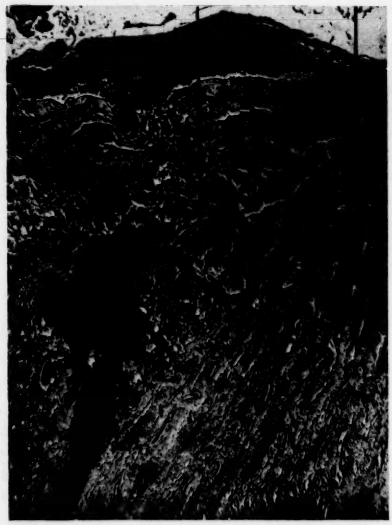

Figure 2. *Low Magnification of the Angioma at the Tip of the Papilla, with Overlying Blood Clot.*

I saw a blood clot on the upper pyramid in the inferior infundibulum that I could not wash off. Then, I opened the kidney, exposing the upper pole and upper pyramid. It was roughened, but I could not be sure what the nature of it was. Rather than have to reoperate on this kidney, I removed it. My impression was that the patient had a lesion of the upper pyramid.

Dr. Castleman: We very carefully sectioned the kidney, including the area in the upper papilla that Dr. Leadbetter described as being granular. After our routine sections were finished we could find nothing. In fact it was reported as being only inflammation and hemorrhage in the pelvis and the calyxes. Dr. Leadbetter was not satisfied, so we recut the blocks over and over, making nearly serial sections, and finally found the lesion that caused the bleeding.

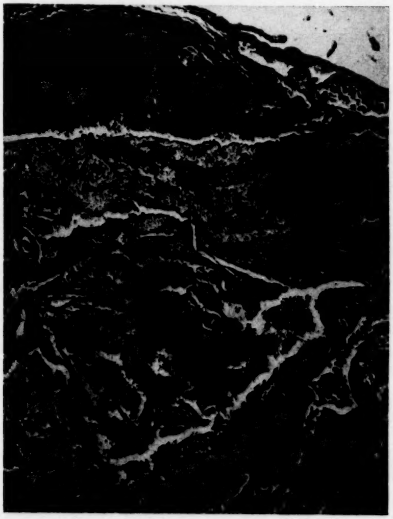

Figure 3. *Higher Magnification of the Blocked Area in Figure 2, Showing Details of the Angioma.*

The clot that Dr. Leadbetter could not wash off covered a small lesion — a tiny angioma, or what might be called a vascular malformation (Fig. 2 and 3). It is possible that many of the cases of idiopathic hematuria are caused by such a lesion. I am sorry to say that at this hospital we have made the diagnosis of idiopathic hematuria on patients who have had exactly the same history and in whose kidneys we have not been able to find a lesion.

Dr. Leadbetter: I should like to point out one thing on the x-ray film because I think that the diagnosis could have been made from it. There is an irregularity of the right superior pyramid, as evidenced by a slight irregular infiltration of pyelographic medium.

CASE 42262

Presentation of Case

First admission. A five-and-a-half-year-old boy was admitted to the hospital because of abdominal pain.

About eight hours previously he noted the onset of persistent, nonradiating, crampy midabdominal pain and nausea; he vomited and passed a normal-appearing stool. The pain became more severe in the lower middle portion of the abdomen, and the temperature rose to 103°F. There were seven episodes of vomiting up until the time of admission. A small, loose, yellow stool was passed five hours before entry. There was no urinary frequency or dysuria.

Figure 1. *Opaque Cystogram, Taken with the Patient Rotated Slightly to the Right, Showing Indentation on the Right Superior Aspect of the Bladder (Arrows).*

Physical examination showed a well developed, well nourished boy complaining of intermittent abdominal cramps. There was tenderness in both lower quadrants of the abdomen, more marked on the right. No organs or masses were palpable. One observer noted diffuse rebound tenderness. There was voluntary spasm in the right lower quadrant. Bowel sounds were active. Rectal examination was negative. The testes were in the scrotum.

The temperature was 100.8°F. by rectum, the pulse 100, and the respirations 24. The blood pressure was 70 systolic, 50 diastolic.

Examination of the blood revealed a hemoglobin of 12.4 gm. per 100 ml. and a white-cell count of 25,000, with 91 per cent neutrophils. The urine was normal. Stool cultures were negative for enteric pathogens.

The temperature rose to 106.2°F. by rectum, on the first hospital day. With alcohol sponge baths, fluids given orally and intravenously and salicylates the temperature fell to normal and the white-cell count, which had risen to 35,600 on the first hospital day, fell to 19,000. No definite right-lower-quadrant localization of pain or rebound or cough tenderness was observed. There were occasional bursts of peristalsis. The abdominal pain subsided, but the patient still noted discomfort when changing position. Some loose stools were passed. The condition improved, and he was discharged on the fourth hospital day, feeling well.

Second admission (five months later). In the interval the patient remained well, and the white-cell count fell to normal. Seventeen days before admission the abdominal pain, associated with much vomiting, recurred and lasted for three days. There was a normal bowel movement at this time. After laxatives the stools were loose. One week before entry he noted persistent severe burning suprapubic pain associated with urination. At the time of admission he was unable to empty the bladder because of the pain. The urine appeared grossly normal. Bowel movements were normal in frequency and unassociated with pain; the stools were normal in color. The presence of fever, chills, nausea, vomiting and anorexia was denied. There was no back pain or narrowing of the urinary stream. The patient had been kicked in the groin by his brother four weeks previously, without apparent sequelae.

Physical examination showed the patient to be in no distress. There was guarding of the lower abdomen, which was diffusely tender. Voluntary spasm of the rectus muscles inferior to the umbilicus was noted. A suprapubic mass extended from midway to the umbilicus to the pubis. Dullness to percussion and marked tenderness were present in the region of the mass, which could be felt on rectal examination.

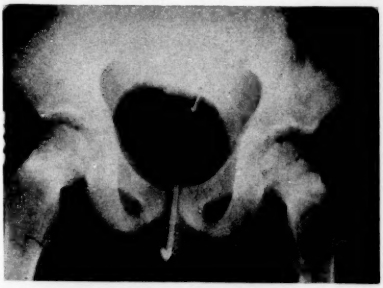

Figure 2. *Air Cystogram, Showing a Similar Extrinsic Pressure Deformity of the Bladder (Arrow).*

The temperature was 103°F., the pulse 120, and the respirations 24. The blood pressure was 112 systolic, 68 diastolic.

The sediment of a specimen of urine obtained by catheterization contained 0 to 2 white cells per high-power field; culture showed no growth. Examination of the blood revealed a hematocrit of 36 per cent and a white-cell count of 25,200, with 85 per cent neutrophils. The nonprotein nitrogen was 23 mg. per 100

ml. An abdominal x-ray film was normal except for an anomalous vertebra at the lumbosacral junction. An intravenous pyelogram showed normal kidney outlines although the right renal calyceal system was not ideally visualized; the psoas shadows appeared normal. On the cystograms there was a constant impression on the right superior surface of the bladder; no definite intraluminal mass was seen in the bladder (Fig. 1 and 2).

On the third hospital day an operation was performed.

Differential Diagnosis

Dr. William Ketchum*: At the time of the first admission the staff decided that the patient did not have acute appendicitis and elected to treat him symptomatically. I think that they must have been somewhat worried by the events that transpired, because a temperature of 106.2°F. is high even for a five-year-old boy. Were blood cultures taken or antibiotics given?

Dr. Winfield S. Morgan: Blood culture was not done; antibiotics were not given.

Dr. Ketchum: As I try to reconstruct this, the surgeons watched the patient while trying to decide whether there was an acute abdominal condition and whether they should operate, but they were never able to localize tenderness in the right lower quadrant. There were "occasional bursts of peristalsis" so that there was probably no ileus.

If I am allowed, I should like to ask what the "sign-out" diagnosis was, on the first admission. I assume that it was "acute gastroenteritis."

Dr. Morgan: "Abdominal pain of unknown etiology."

Dr. Ketchum: Were any studies done in the interim, such as urinary tests, a gastrointestinal series or barium-enema examination?

Dr. Joseph Hanelin: No.

Dr. Ketchum: At the time of the second admission the staff evidently was bothered about whether the boy had a genitourinary abnormality. I think they were probably considering a ureterocele or a diverticulum of the bladder. May I see the x-ray films?

Dr. Hanelin: All the films were made at the last admission. The preliminary film of the abdomen shows scattered gas in the bowel, without abnormal distention. I am unable to define the mass that was felt very clearly; there is a vague suggestion of a density within the true pelvis. The renal and psoas shadows were described as normal although the right psoas is not easily traced. The pyelogram demonstrates normal excretion bilaterally, without evidence of ureteral obstruction or displacement. In the cystogram done with opaque material (Fig. 1) and with air (Fig. 2) there is no intrinsic lesion of the bladder, but there is evidence of extrinsic pressure on the right superior aspect of the bladder (Fig. 2).

Dr. Ketchum: Is there any suggestion of a calcified fecalith?

Dr. Hanelin: No; I am unable to see any calcification.

Dr. Ketchum: Would you say the pattern of the large bowel was normally placed?

Dr. Hanelin: I looked at these films with that in mind but could not be sure that there was any displacement of the air-filled bowel.

Dr. Ketchum: Is there malrotation?

Dr. Hanelin: I see no evidence of malrotation.

Dr. Ketchum: I am as certain as I can be of anything that at operation a pelvic abscess was found. This, I believe, was secondary to an inflammatory lesion associated with the gastrointestinal tract. Having stuck my neck out to this limited extent, I shall now try to piece the findings together to ascertain the cause of the abscess. One would be rather foolhardy not to place acute appendicitis at the top of the list, although many features of this case are atypical. In a child of this age it is extremely difficult to localize tenderness — in fact to be certain that there is tenderness. This child was apparently quite stoic; I have the impression that he did not complain a great deal. If he had complained more of tenderness or pain he might have been operated on at the time of the first admission. I certainly think an operation would have been justified at that time, in spite of the facts that the pain was crampy rather than steady and that it was difficult to localize tenderness. Rebound tenderness is very difficult to evaluate in a youngster of this age because it is hard to tell whether it hurts when pressure is exerted or when it is released. I assume that he had an acute suppurative appendicitis, which subsided. Possibly there was a small rupture that was walled off locally by a periappendiceal reaction. I had hoped that antibiotics had been given, because this would have fitted in more readily with my impression.

If I assume that he had appendicitis, I must also assume that he had a recurrence. Whether the laxatives given produced a rupture of a gangrenous appendix I do not know, but such a series of events would account for the appearance of an abscess in the pelvis.

When one thinks about the appendix in a child, one also has to think about a Meckel diverticulum. Disease in it can produce an identical picture; what I have said about appendicitis could also be said about Meckel's diverticulitis. If there had been an inflammation in a Meckel diverticulum, there might have been an associated, incomplete intussusception to account for the crampy pain. Again, I should have to assume that the infection subsided and then recurred, with gangrene and abscess formation.

I have ruled out acute pancreatitis, which is extraordinarily rare in children. Acute primary perito-

*Clinical associate in children's medicine, Massachusetts General Hospital.

nitis also is extremely uncommon except in the presence of nephrosis or some other condition that debilitates the patient.

I doubt if the lesion had obstructed the intestines to a marked degree because there was no abdominal distention and the vomiting was apparently not protracted or suggestive of obstruction. Other lesions that should be mentioned, however, are internal hernias, in which the bowel is incarcerated in a peritoneal pocket, volvulus associated with an anomaly in the bowel and intussusception. This boy was too old for intussusception, unless there was an associated anomaly; also, rectal bleeding usually accompanies intussusception.

In conclusion, I suspect that this was a case of acute appendicitis, recurrent, with perforation and abscess formation. To add a little zest, however, I shall suggest that the patient had a duplication in the ileum that communicated with the bowel at one end; that there was inflammation in the duplication; that this produced partial obstruction in the small bowel; and that, because of the way that the vessels characteristically course over a duplication, there was embarrassment of circulation of the bowel (which might have been responsible for the very high white-cell and neutrophil counts, even though there was no blood in the stools). If I make this suggestion I have to assume that the second episode was a recurrence of the inflammation, with gangrene, rupture and formation of an abscess.

DR. JOHN D. CRAWFORD: When this boy was admitted to the hospital for the second time with a week's story of frequent and painful urination, our first thought in the Emergency Ward was that he had an inflammatory lesion obstructing outflow of urine from the bladder. He was catheterized, with recovery of a large volume of urine and considerable relief of pain. It was not noted immediately, but with release of over 300 ml. of urine there was no appreciable diminution in size of the mass. Some hours later reexamination on the ward showed the mass still present. A second catheterization failed to change the findings and yielded clear urine. Because of these observations intravenous pyelograms were immediately obtained and showed the mass to be separate from the bladder. An exploratory operation was then recommended by the Service with the expectation that the two best possibilities were urachal cyst and appendiceal abscess.

CLINICAL DIAGNOSIS

? Infected urachal cyst.
? Appendiceal abscess.

DR. WILLIAM KETCHUM'S DIAGNOSIS

Duplication of ileum, with perforation and formation of pelvic abscess.
? Acute appendicitis, recurrent, with abscess formation.

ANATOMICAL DIAGNOSIS

Acute appendicitis, with perforation and abscess formation.

PATHOLOGICAL DISCUSSION

DR. JACK E. TETIRICK: At the time of operation the incision was placed in the mid-line suprapubically; we dissected only into the subcutaneous tissue in the mid-line, suspecting originally that the patient had an infected urachal cyst. When we dissected to this depth, it was obvious that the mass was suprapubic within the peritoneal cavity; therefore, we opened the peritoneum through the same incision. We found a pelvic abscess in a somewhat unusual position; it lay anteriorly against the anterior wall of the abdomen at the brim of the pelvis. Its anterior inferior margin was the part of the bladder in which the deformity had been seen in the x-ray film. The medial and superior aspect of the abscess was formed by the small bowel, a loop of which was densely adherent to the abscess. The main abscess mass also involved the cecum and terminal ileum. We therefore resected the abscess en bloc. It was possible after it had been freed from the adherent structures to identify the base of the appendix, which was not unduly inflamed and could be turned in. The distal end of the appendix extended into the abscess and was completely destroyed. After we had removed the mass, inspection of the bowel revealed a granuloma lying along the wall of the bowel that had been adherent to the abscess. Therefore, this portion of the small bowel was resected.

DR. MORGAN: The microscopical sections showed the typical picture of acute and chronic inflammation, with abscess formation characteristic of an appendiceal abscess. In addition there was a great deal of old scar tissue that, I think, was older than seventeen days; therefore, there probably had been some rupture during the initial episode.

DR. RICHARD C. AUSTIN: In answer to Dr. Ketchum's comments about the first admission, I should like to elaborate and defend our actions somewhat. In retrospect he almost certainly had appendicitis at that time. We naturally were very much concerned about him and watched him closely with the Pediatric Service. The white-cell count and temperature were always inconsistently high as compared with the abdominal findings. At no time did he demonstrate cough or rebound tenderness, nor did the tenderness or guarding ever localize clearly. He moved around in bed actively, was hungry, had hyperactive peristalsis and never seemed to have generalized peritonitis. He improved very rapidly.

At the second admission we were asked to see him on the second day, when he was again eating well. The location of the mass and the prominence of urinary symptoms led us to the erroneous diagnosis of infected urachal cyst.

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PROPHYLACTIC USE OF ANTIBIOTICS IN PROSTATIC SURGERY

MANY physicians and surgeons firmly believe that the routine prophylactic use of antibiotics will avert or reduce the incidence and severity of bacterial infections in patients in whom such invasions can be expected to occur postoperatively or as a complication of other diseases. That this belief is often unjustified has been adequately demonstrated in recent studies, both by Lepper and his co-workers in Chicago and by Weinstein in Boston, in cases of measles and in tracheotomized patients with poliomyelitis. Their studies, which have previously been commented on in these columns, have shown clearly that pathogenic bacteria are implanted as frequently in the respiratory tract of prophylactically treated patients as in those not treated with antibiotics. However, in the former the bacterial strains encountered are usually resistant, both in vitro and in vivo, to the antibiotics thus given, whereas the organisms cultured from previously untreated patients are more often sensitive to the commonly used agents, and the resulting infections are more likely to respond favorably to treatment.

Surgeons sometimes speak of operating "under an umbrella of antibiotics," as though such an umbrella will hold back or somehow divert the flood of bacteria from the operative field. Adequately controlled studies to justify confidence in this measure are woefully lacking, however, particularly since the use of antibiotics has become widespread. Any careful evaluation of this practice is therefore welcome.

Such a study dealing with the prophylactic use of chloramphenicol in patients undergoing transurethral resections of the prostate gland has recently been reported from Milwaukee by Appleton and Waisbren.* These workers gave the antibiotic in strict alternation to 50 of 100 consecutive patients undergoing this operation. They could demonstrate no significant effect from the treatment on the immediate postoperative complications, pyrexia, bacteremia, urine cultures, drainage period or hospital stay or on the mortality. The authors therefore believed that their study did not provide evidence to justify the prophylactic use of antibiotics in transurethral prostatectomy.

Of interest was the fact that a completely sterile specimen of urine was not obtained from a single patient in either group. Almost identical numbers of patients in each group harbored *Micrococcus pyogenes, Escherichia coli, Proteus vulgaris* and *Pseudomonas aeruginosa*, which were the most important pathogens isolated. Moreover, the pathogenic organisms isolated from cultures of the blood of 4 treated patients in the immediate postoperative period were *Esch. coli*, whereas blood cultures similarly obtained in 2 untreated patients yielded *Ps. aeruginosa* and coagulase positive *M. aureus* — species of bacteria

*Appleton, D. M., and Waisbren, B. A. Prophylactic use of chloramphenicol in transurethral resection of prostate gland. *J. Urol.* **75**: 304-313, 1956.

that are notoriously resistant to antibiotics that are widely used.

It appears, therefore, that in this instance, as in the others mentioned, the antibiotic umbrella may have held back the antibiotic-susceptible bacteria and permitted the resistant ones to pass through.

REGARDING THINGS AND THE POSSESSION OF THEM

Certified Milk ("The Magazine of Quality Milk"), in its issue for January, 1956, beginning its thirty-first year of publication, demonstrates unusual promise for the continued success of such periodical literature, if not of certified milk itself. Not only are the relations dependent on social dominance in a modern dairy herd subjected to an up-to-date psychologic appraisal, but the future of industry in general and of American life in particular is thoroughly portrayed.

The study on social-dominance relations was conducted at the Iberian Livestock Experimental Station at Jeanerette, Louisiana; it is only remotely reminiscent of Julius Caesar's expressed preference for the mayoralty of a little Iberian village to the second position in all Rome. In this investigation the relatively passive butting, the more or less active fighting and the practice of grazing as a possible displacement activity were carefully observed, leading to the conclusion that the social behavior of cattle is in few ways superior to that of their human counterparts. Despite the so-called bovine temperament even lactating cows are not always contented.

Elsewhere in the January issue of *Certified Milk* various business leaders predict for the land of the free and the home of the brave a push-button wonderland in which Americans, by 1975, "will earn more, work less and stop worrying about their material wants." With apologies to Mr. Alfred Noyes they will then wander hand in hand in a push-button wonderland, their material desires satisfied and their spiritual needs no doubt forgotten. As Senator McMahon is quoted as saying, "We already have the buttons" although during the recent snows of March the general observation was that the necessity for push exceeded the supply of buttons, discounting those that were busted in the process.

Some typical prognostications of the high estate that man will reach in 1975 were offered by these captains of industry, such as 80,000,000 fine motor cars instead of today's 50,000,000 fine motor cars, a society in which material welfare will cease to be a problem and a rapid increase in population will keep pace with a constant flow of new products, characterized as a merchant's dream. Various corporation presidents expressed their tempered optimism for nineteen years hence, as follows: at least 92,000,000 TV sets, . . . 90 per cent of which will feature color; solar-powered transistor radios that will last a lifetime; guided robot missiles to land on planets and having landed to transmit back to earth television pictures of the local scenery; automobiles powered by nuclear energy. Gloriously and finally, "It is difficult to be anything but confident and optimistic about the future."

MEDICAL EDUCATION AND THE COMMONWEALTH FUND

THE Commonwealth Fund of New York announced late in May further unrestricted grants of $4,850,000 from capital assets and current income to seven university medical schools. These grants bring to a total of $12,600,000 the gifts made by this Fund since November, 1955, to strengthen medical education, and are in addition to the grants made for specific projects in medical education during the fiscal year 1955-1956.

Although the need "for funds for strengthening faculty and raising teaching salaries, clarifying educational objectives, reviewing curriculums and restructuring programs of medical education" was in mind, no restrictions were placed on the use of these gifts.

On the New England scene, Harvard and Yale were beneficiaries of the original appropriations made on November 28, 1955, and Tufts University School of Medicine shared in the disbursement of February, 1956. It is gratifying to learn that Boston University School of Medicine is benefiting from the most recent allocation of Commonwealth funds to the extent of a $600,000 grant.

ARMY APPROVES FLUORIDATION

AT the time of the American Civil War, one reads, prospective candidates for the Union Army were disqualified for service on the firing line if they lacked certain natural strategic dental equipment. These teeth were needed to tear open a form of paper cartridge current at the time, and it is said that occasionally representatives of Northern manhood, to avoid the draft, had them extracted, though otherwise healthy.

It would appear that the Army, in authorizing the fluoridation of drinking water at 21 posts in the United States, Alaska, Hawaii and Puerto Rico, had in mind the indispensability to the soldier in 1861 of a certain number of sound opposing teeth, were it not for the fact that the presence on the post of a quota of children below military age is an essential requirement for the fluoridation.

The dental requirements of an army as they apply

to nutrition are so well known that no obsolete practices associated with rapid fire need to be invoked today. The Medical and Dental Corps are well alerted by such aphorisms as that of Napoleon, that an army marches on its stomach, or Grant's terse statement that in the Great Rebellion beans killed more soldiers than did bullets.

Perhaps the necessity of healthy teeth to a nation's future soldiery has had some influence on the more vigorous of the opponents of fluoridation in general, and the Army's approval of the practice may still further strengthen their opposition.

Messrs. Editors,—*Allow me, through you, to call the attention of the profession to an article of practical utility in the dietetic treatment of disease. It is the "Essence of Rennet," prepared by Simon, apothecary, of Berlin, for making Swiss whey...*

Boston M. & S. J. *July 3, 1856*

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Rheumatic Heart Disease, with Decompensation

A twenty-seven-year-old gravida IV, para II, died of cardiac decompensation in the fifth month of pregnancy.

She had had acute rheumatic fever at five and again at six, and chorea at twelve years of age. The first pregnancy, when she was nineteen, was complicated only by dyspnea and ankle edema at term. During the second pregnancy, at the age of twenty-three, acute failure in the sixth month was apparently precipitated by an upper respiratory infection and further complicated by a profound secondary anemia — the hemoglobin was reported to be 53 per cent (Sahli). Fortunately, she miscarried and recovered. At twenty-four years of age a valvuloplasty was performed, and her third pregnancy was successfully completed two years later without decompensation or any distress.

The current pregnancy was marked by coughing and dyspnea on exertion beginning in the fourth month. Two weeks later, fever and hemoptysis developed, and the patient was admitted to the hospital with a temperature of 104°F., a pulse of 140 and respirations of 40; the blood pressure was 110 systolic, 80 diastolic. She was in acute dyspnea and orthopnea, with paroxysms of coughing and hemoptysis. Pulsating distended neck veins and rales throughout both lungs were present. Examination suggested a recurrence of mitral stenosis, and an electrocardiogram was consistent with hypertrophy of the right ventricle.

Despite sodium restriction and digitalis, pulmonary edema persisted for eight days but then improved slightly. Oxygen was also instilled nasally, and tourniquets applied intermittently to the extremities. However, on the ninth day, the blood pressure suddenly failed. Despite the usual emergency measures, the patient rapidly failed and died.

Autopsy revealed marked mitral stenosis, a healed surgical wound at the atrial appendage, the usual findings of right-sided heart failure and a normal eighteen weeks' pregnancy.

This case was classified as a preventable death with the responsibility, however, assigned to the patient herself. The cause of death, of course, was rheumatic heart disease, with decompensation and pregnancy. Opinion was not unanimous in this classification, however, one physician taking the position that it was a nonpreventable death from the point of view of those who were presented with the problem at the time of final admission. This difference of opinion, however, is merely technical since it was unanimously agreed that her treatment was of a high order of skill and that nothing further could have been done to prevent her death under the circumstances. Preventability, however, can honestly be assigned to a patient who had had a great deal of medical care in her time and who certainly knew that she should have consulted physicians far earlier in pregnancy. She had been stringently advised not to get pregnant again. She chose to disregard this advice for reasons that may have seemed sufficient to her but ultimately proved lethal. A number of cases not dissimilar to this have recently been reported in which patients with mitral stenosis have been operated upon after a difficult or unsuccessful pregnancy. They then seem, because of their improved subjective state, to become very much overconfident and not only undertake inadvisable pregnancies but also, once pregnant, disregard the usual basic precautionary rules for all pregnant women and especially for those with heart disease. This is in part, perhaps, the fault of the medical profession for not sufficiently impressing patients, especially those who have had valvulotomy, with the gravity of their condition. In any event, it seems apparent that with the proper prenatal care this patient might well have gone through the pregnancy or, at the very worst, would have had the opportunity for interruption and sterilization before getting into the serious condition that existed on admission.

John Figgis Jewett, M.D.
Chairman

BLUE CROSS–BLUE SHIELD

BLUE SHIELD DIAGNOSTIC RIDER

On July 1, 1956, the following major changes in the Blue Shield Diagnostic Rider will be effected:

All benefits for laboratory determinations will be deleted.

Full credit for x-ray examinations will be limited to those undertaken within forty-eight hours of an accident, those required to check the course of a recent fracture and those done in conjunction with major endoscopy.

The payment formula for partial-credit x-ray examinations will be modified as follows:

For x-ray examinations undertaken during any period of 30 consecutive days Blue Shield will pay the difference between $15 and the total amount derived from the Blue Shield Schedule of Fees provided the total amount is less than $30. If the total amount derived from the Blue Shield Schedule of Fees is $30 or more, Blue Shield will pay 50 per cent of the total amount.

All distinctions in fees between general practitioners and specialists will be abolished.

The following two regulations instituted under the original Rider will remain in force under the new Rider:

No benefits will be provided for x-ray examinations undertaken for other than acute traumatic conditions by any physician who has purchased x-ray equipment since September 1, 1955, unless the physician can produce evidence of formal training in radiology.

In all cases the physician who interprets an x-ray film or who carries out a fluoroscopy must submit the Blue Shield Medical Service Report in his name regardless of who actually takes the x-ray film.

Experience obtained since September 1, 1955, when the original rider first went into effect seems to warrant the following observations:

The benefits provided for laboratory determinations were of small significance because the deductible of $10 usually left little for Blue Shield to pay.

There was virtually no call for full-credit x-ray studies after discharge from the hospital to determine the current status of the condition treated in the hospital.

Full-credit x-ray examinations for pelvimetry were very common, with the result that normal obstetric costs, which bulk large in any prepayment program, were being increased disproportionately.

By far the greatest number of x-ray films were taken by specialists, and this was particularly true of partial-credit x-ray examinations.

The hope that the number of Blue Cross diagnostic admissions would decrease was not realized.

Although it was possible, upon payment of $15, for a patient to receive $60 worth of partial-credit x-ray films, the over-all average consistently ran between $30 and $35.

The experience was about what had been anticipated.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date		Clinic Consultant
Salem	July	2	Paul W. Hugenberger, M.D.
Gardner	July	9	Carter R. Rowe, M.D.
Lynn*	July	9	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Haverhill	July	11	William T. Green, M.D., and Henry Banks, M.D.
Brockton	July	12	George W. Van Gorder, M.D.
Pittsfield	July	18	Edward J. Coughlin, Jr., M.D.
Worcester	July	20	John W. O'Meara, M.D.
Hyannis	July	26	Paul L. Norton, M.D.
Greenfield	August	2	Charles L. Sturdevant, M.D.
Lowell	August	3	Albert H. Brewster, M.D.
Fall River	August	27	David S. Grice, M.D., and Arthur W. Trott, M.D.
Springfield	August	28	James D. Fisher, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	July 3, 10, 17, 24, 31
Fitchburg	July 11, 18, 25

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D., and Joseph E. Murray, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Prenatal and Paranatal Factors in the Development of Childhood Behavior Disorders. By Martha E. Rogers, Sc.D., professor of nursing education, School of Education, New York University; Abraham M. Lilienfeld, M.D., chief, Department of Statistics and Epidemiological Research, Roswell Park Memorial Institute, Buffalo, New York; and Benjamin Pasamanick, M.D., professor of psychiatry, Ohio State University College of Medicine, and director of research, Columbus State Psychiatric Institute. 8°, paper, 157 pp., with 4 illustrations and 124 tables. Baltimore: Johns Hopkins University, School of Hygiene and Public Health, 1956.